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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 215/38, 241/44, 277/72, A61K 31/47, 31/495, 31/425 — A2

(11) International Publication Number: WO 99/26927

(43) International Publication Date: 3 June 1999 (03.06.99)

(21) International Application Number: PCT/US98/24833

(22) International Filing Date: 20 November 1998 (20.11.98)

(30) Priority Data:
60/066,758 21 November 1997 (21.11.97) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 60/066,758 (CIP)
Filed on 21 November 1997 (21.11.97)

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS FOR TREATING CENTRAL NERVOUS SYSTEM DISEASES

(57) Abstract

The present invention provides compounds, and pharmaceutical compositions containing those compounds, that act as antagonists at metabotropic glutamate receptors. The compounds are useful for treating neurological diseases and disorders. Methods of preparing the compounds also are disclosed.

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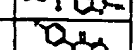
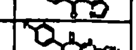
2	
3	
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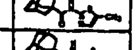
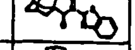
8	
9	
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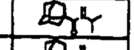
11	
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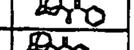
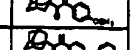
13	
14	
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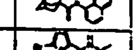
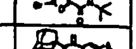
21	
22	
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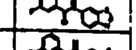
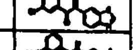
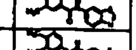
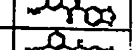
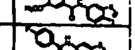
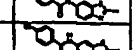
25	
26	
27	
28	
29	
30	
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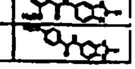
33	

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METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS FOR TREATING CENTRAL NERVOUS SYSTEM DISEASES

FIELD OF THE INVENTION

The present invention provides compounds active at metabotropic glutamate receptors and that are useful for treating neurological and psychiatric diseases and disorders.

BACKGROUND OF THE INVENTION

Recent advances in the elucidation of the neurophysiological roles of metabotropic glutamate receptors have established these receptors as promising drug targets in the therapy of acute and chronic neurological and psychiatric disorders and diseases. However. the major challenge to the realization of this promise has been the development of metabotropic glutamate receptor subtype-selective compounds.

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system (CNS). Glutamate produces its effects on central neurons by binding to and thereby activating cell surface receptors. These receptors have been divided into two major classes, the ionotropic and metabotropic glutamate receptors, based on the structural features of the receptor proteins, the means by which the receptors transduce signals into the cell, and pharmacological profiles.

The metabotropic glutamate receptors (mGluRs) are G protein-coupled receptors that activate a variety of intracellular second messenger systems following the binding of glutamate. Activation of mGluRs in intact mammalian neurons elicits one or more of the following responses: activation of phospholipase C: increases in phosphoinositide (PI) hydrolysis: intracellular calcium release: activation of phospholipase D: activation or inhibition of adenyl

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cyclase: increases or decreases in the formation of cyclic adenosine monophosphate (cAMP); activation of guanylyl cyclase: increases in the formation of cyclic guanosine monophosphate (cGMP); activation of phospholipase A_2: increases in arachidonic acid release: and increases or decreases in the activity of voltage- and ligand-gated ion channels. Schoepp *et al.*, *Trends Pharmacol. Sci. 14*:13 (1993); Schoepp, *Neurochem. Int. 24*:439 (1994); Pin *et al.*, *Neuropharmacology 34*:1 (1995).

Eight distinct mGluR subtypes, termed mGluR1 through mGluR8, have been identified by molecular cloning. *See, for example,* Nakanishi. *Neuron 13*:1031 (1994); Pin *et al.*, *Neuropharmacology 34*:1 (1995); Knopfel *et al.*, *J. Med. Chem. 38*:1417 (1995). Further receptor diversity occurs via expression of alternatively spliced forms of certain mGluR subtypes. Pin *et al.*, *PNAS 89*:10331 (1992); Minakami *et al.*, *BBRC 199*:1136 (1994); Joly *et al.*, *J. Neurosci. 15*:3970 (1995).

Metabotropic glutamate receptor subtypes may be subdivided into three groups, Group I, Group II, and Group III mGluRs, based on amino acid sequence homology, the second messenger systems utilized by the receptors. and by their pharmacological characteristics. Nakanishi. *Neuron 13*:1031 (1994); Pin *et al.*, *Neuropharmacology 34*:1 (1995); Knopfel *et al.*, *J. Med. Chem. 38*:1417 (1995).

Group I mGluRs comprise mGluR1. mGluR5. and their alternatively spliced variants. The binding of agonists to these receptors results in the activation of phospholipase C and the subsequent mobilization of intracellular calcium. Electrophysiological measurements have been used to demonstrate these effects in, for example, *Xenopus* oocytes expressing recombinant mGluR1 receptors. *See, for example* Masu *et al.*, *Nature 349*:760 (1991); Pin *et al.*, *PNAS 89*:10331 (1992). Similar results have been achieved with oocytes expressing recombinant mGluR5 receptors. Abe *et al.*, *J. Biol. Chem. 267*:13361 (1992); Minakami *et al.*, *BBRC 199*:1136 (1994); Joly *et al.*, *J. Neurosci. 15*:3970 (1995). Alternatively, agonist activation of recombinant mGluR1 receptors expressed in Chinese hamster ovary (CHO) cells stimulates PI hydrolysis, cAMP formation. and arachidonic acid release as measured by standard biochemical assays. Aramori *et al.*, *Neuron 8*:757 (1992).

In comparison, activation of mGluR5 receptors expressed in CHO cells stimulates PI hydrolysis and subsequent intracellular calcium transients, but no stimulation of cAMP formation or arachidonic acid release is observed. Abe *et al.*, *J. Biol. Chem. 267*:13361 (1992). However, activation of mGluR5 receptors expressed in LLC-PK1 cells results in PI hydrolysis and increased cAMP formation. Joly *et al.*, *J. Neurosci. 15*:3970 (1995). The agonist potency profile for Group I mGluRs is quisqualate > glutamate = ibotenate > *(2S,1'S,2'S)*-2-carboxycyclopropyl)glycine (L-CCG-I) > *(1S,3R)*-1-aminocyclopentane-1,3-dicarboxylic acid (ACPD). Quisqualate is relatively selective for Group I receptors, as compared to Group II and Group III mGluRs, but it also is a potent activator of ionotropic AMPA receptors. Pin *et al.*, *Neuropharmacology 34*:1, Knopfel *et al.*, *J. Med. Chem. 38*:1417 (1995).

The lack of subtype-specific mGluR agonists and antagonists has impeded elucidation of the physiological roles of particular mGluRs, and the mGluR-associated pathophysiological processes that affect the CNS have yet to be defined. However, work with the available non-specific agonists and antagonists has yielded some general insights about the Group I mGluRs as compared to the Group II and Group III mGluRs.

Attempts at elucidating the physiological roles of Group I mGluRs suggest that activation of these receptors elicits neuronal excitation. Various studies have demonstrated that ACPD can produce postsynaptic excitation upon application to neurons in the hippocampus, cerebral cortex, cerebellum, and thalamus, as well as other brain regions. Evidence indicates that this excitation is due to direct activation of postsynaptic mGluRs, but it also has been suggested that activation of presynaptic mGluRs occurs, resulting in increased neurotransmitter release. Baskys, *Trends Pharmacol. Sci. 15*:92 (1992); Schoepp, *Neurochem. Int. 24*:439 (1994); Pin *et al.*, *Neuropharmacology 34*:1(1995).

Pharmacological experiments implicate Group I mGluRs as the mediators of this excitatory mechanism. The effects of ACPD can be reproduced by low concentrations of quisqualate in the presence of iGluR antagonists. Hu *et al.*, *Brain Res. 568*:339 (1991); Greene *et al.*, *Eur. J. Pharmacol. 226*:279 (1992). Two phenylglycine compounds known to activate mGluR1, namely *(S)*-3-hydroxyphenylglycine (*(S)*-3HPG) and *(S)*-3,5-dihydroxyphenylglycine (*(S)*-DHPG), also produce excitation. Watkins *et al.*, *Trends Pharmacol. Sci. 15*:33

(1994). In addition, the excitation can be blocked by *(S)*-4-carboxyphenylglycine (*(S)*-4CPG), *(S)*-4-carboxy-3-hydroxyphenylglycine (*(S)*-4C3HPG), and (+)-alpha-methyl-4-carboxyphenylglycine ((+)-MCPG), compounds known to be mGluR1 antagonists. Eaton *et al.*, *Eur. J. Pharmacol. 244*:195 (1993); Watkins *et al.*, *Trends Pharmacol. Sci. 15*:333 (1994).

Metabotropic glutamate receptors have been implicated in a number of normal processes in the mammalian CNS. Activation of mGluRs has been shown to be required for induction of hippocampal long-term potentiation and cerebellar long-term depression. Bashir *et al.*, *Nature 363*:347 (1993); Bortolotto *et al.*, *Nature 368*:740 (1994); Aiba *et al.*, *Cell 79*:365 (1994); Aiba *et al.*, *Cell 79*:377 (1994). A role for mGluR activation in nociception and analgesia also has been demonstrated. Meller *et al.*, *Neuroreport 4*: 879 (1993). In addition, mGluR activation has been suggested to play a modulatory role in a variety of other normal processes including synaptic transmission, neuronal development, apoptotic neuronal death, synaptic plasticity, spatial learning, olfactory memory, central control of cardiac activity, waking, motor control, and control of the vestibulo-ocular reflex. For reviews, see Nakanishi, *Neuron 13*: 1031 (1994); Pin *et al.*, *Neuropharmacology 34*:1; Knopfel *et al.*, *J. Med. Chem. 38*:1417 (1995).

Metabotropic glutamate receptors also have been suggested to play roles in a variety of pathophysiological processes and disease states affecting the CNS. These include stroke, head trauma, anoxic and ischemic injuries, hypoglycemia, epilepsy, and neurodegenerative diseases such as Alzheimer's disease. Schoepp *et al.*, *Trends Pharmacol. Sci. 14*:13 (1993); Cunningham *et al.*, *Life Sci. 54*:135 (1994); Hollman *et al.*, *Ann. Rev. Neurosci. 17*:31 (1994); Pin *et al.*, *Neuropharmacology 34*:1 (1995); Knopfel *et al.*, *J. Med. Chem. 38*:1417 (1995). Much of the pathology in these conditions is thought to be due to excessive glutamate-induced excitation of CNS neurons. Because Group I mGluRs appear to increase glutamate-mediated neuronal excitation via postsynaptic mechanisms and enhanced presynaptic glutamate release, their activation probably contributes to the pathology. Accordingly, selective antagonists of Group I mGluR receptors could be therapeutically beneficial, specifically as neuroprotective agents or anticonvulsants.

Preliminary studies assessing therapeutic potentials with the available mGluR agonists and antagonists have yielded seemingly contradictory results. For example, it has been reported that application of ACPD onto hippocampal neurons leads to seizures and neuronal damage (Sacaan *et al.*, *Neurosci. Lett.* *139*:77 (1992); Lipparti *et al.*, *Life Sci.* *52*:85 (1993). Other studies indicate, however, that ACPD inhibits epileptiform activity, and also can exhibit neuroprotective properties. Taschenberger *et al.*, *Neuroreport* *3*:629 (1992); Sheardown, *Neuroreport* *3*:916 (1992); Koh *et al.*, *Proc. Natl. Acad. Sci. USA* *88*:9431 (1991); Chiamulera *et al.*, *Eur. J. Pharmacol.* *216*:335 (1992); Siliprandi *et al.*, *Eur. J. Pharmacol.* *219*:173 (1992); Pizzi *et al.*, *J. Neurochem.* *61*:683 (1993).

It is likely that these conflicting results are due to the lack of selectivity of ACPD, which causes activation of several different mGluR subtypes. In the studies finding neuronal damage it appears that Group I mGluRs were activated, thereby enhancing undesirable excitatory neurotransmission. In the studies showing neuroprotective effects it appears that activation of Group II and/or Group III mGluRs occurred, inhibiting presynaptic glutamate release, and diminishing excitatory neurotransmission.

This interpretation is consistent with the observation that *(S)*-4C3HPG, a Group I mGluR antagonist and Group II mGluR agonist, protects against audiogenic seizures in DBA/2 mice, while the Group II mGluR selective agonists DCG-IV and L-CCG-I protect neurons from NMDA- and KA-induced toxicity. Thomsen *et al.*, *J. Neurochem.* *62*:2492 (1994); Bruno *et al.*, *Eur. J. Pharmacol.* *256*:109 (1994); Pizzi *et al.*, *J. Neurochem.* *61*:683 (1993).

Based on the foregoing, it is clear that currently available mGluR agonists and antagonists have limited value, due to their lack of potency and selectivity. In addition, most currently available compounds are amino acids or amino acid derivatives that have limited bioavailabilities, thereby hampering *in vivo* studies to assess mGluR physiology, pharmacology and their therapeutic potential. Compounds that selectively inhibit activation of metabotropic glutamate receptor Group I subtypes should be useful for treatment of neurological disorders and diseases such as senile dementia, Parkinson's disease, Alzheimer's disease, Huntington's Chorea, pain, epilepsy, head trauma, anoxic and ischemic injuries, and psychiatric disorders such as schizophrenia and depression.

It is apparent, therefore, that identification of potent mGluR agonists and antagonists with high selectivity for individual mGluR subtypes, particularly for Group I receptor subtypes, are greatly to be desired.

SUMMARY OF THE INVENTION

It is an object of the present invention, therefore, to identify metabotopic glutamate receptor-active compounds which exhibit a high degree of potency and selectivity for individual metabotropic glutamate receptor subtypes, and to provide methods of making these compounds.

It is a further object of this invention to provide pharmaceutical compositions containing compounds which exhibit a high degree of potency and selectivity for individual metabotropic glutamate receptor subtypes, and to provide methods of making these pharmaceutical compositions.

It is yet another object of this invention to provide methods of inhibiting activation of an mGluR Group I receptor, and of inhibiting neuronal damage caused by excitatory activation of an mGluR Group I receptor.

It is still another object of the invention to provide methods of treating a disease associated with glutamate-induced neuronal damage.

To accomplish these and other objectives, the present invention provides potent antagonists of Group I metabotropic glutamate receptors. These antagonists may be represented by the formula I.

$$R-[\text{Linker}]-Ar$$

wherein R is an optionally substituted straight or branched chain alkyl, arylalkyl, cycloalkyl, or alkylcycloalkyl group containing 5-12 carbon atoms. Ar is an optionally substituted aromatic, heteroaromatic, arylalkyl, or heteroaralkyl moiety containing up to 10 carbon atoms and up to 4 heteroatoms, and [linker] is $-(CH_2)_n-$, where n is 2-6, and wherein up to 4 CH_2 groups may independently be substituted with groups selected from the group consisting of C_1-C_3 alkyl, CHOH, CO, O, S, SO, SO_2, N, NH, and NO. Two heteroatoms in the [linker] may not be adjacent except when those atoms are both N or are both NH. Two adjacent CH_2 groups in [linker] also may be replaced by a substituted or unsubstituted alkene or alkyne group. Pharmaceutically acceptable salts of the compounds also are provided.

In one embodiment of the invention. Ar comprises a ring system selected from the group consisting of benzene. thiazole. furyl, pyranyl. 2H-pyrrolyl. thienyl, pyrrolyl. imidazolyl, pyrazolyl, pyridyl. pyrazinyl, pyrimidinyl, pyridazinyl benzothiazole. benzimidazole. 3H-indolyl. indolyl. indazolyl. purinyl, quinolizinyl. isoquinolyl, quinolyl, phthalizinyl, naphthyridinyl, quinazolinyl. cinnolinyl, isothiazolyl, quinoxalinyl indolizinyl, isoindolyl, benzothienyl, benzofuranyl, isobenzofuranyl, and chromenyl rings. Ar optionally may independently be substituted with up to two C_1-C_3 alkyl groups, or up to two halogen atoms. where halogen is selected from F, Cl, Br, and I.

In another embodiment of the invention, R contains 4. 5, 6, 7. 8. 9. 10 or 11 carbon atoms. where some or all of the hydrogen atoms on two carbon atoms optionally may be replaced with substituents independently selected from the group consisting of F. Cl. OH. OMe. =O, and -COOH.

In yet another embodiment [linker] comprises an amide. ester. or thioester group.

In a preferred embodiment. R comprises a moiety selected from the group consisting of substituted or unsubstituted adamantyl, 2-adamantyl. (1S.2S.3S.5R)-isopinocamphenyl, tricyclo[4.3.1.1(3,8)]undec-3-yl, (1S,2R,5S)-*cis*-myrtanyl. (1R,2R.4S)-isobornyl, (1R.2R.3R.5S)-isopinocamphenyl, (1S.2S.5S)-*trans*-myrtanyl. (1R.2R.5R)-*trans*-myrtanyl, (1R,2S,4S)-bornyl, 1-adamantanemethyl. 3-noradamantyl, (1S.2S.3S.5R)-3-pinanemethyl, cyclooctyl, α.α-dimethylphenethyl, (S)-2-phenyl-1-propyl. cycloheptyl. 4-methyl-2-hexyl groups. 2,2,3,3,4,4,4-heptafluorobutyl. 4-ketoadamantyl, 3-phenyl-2-methylpropyl. 3.5-dimethyladamantyl. *trans*-2-phenylcyclopropyl. 2-methylcyclohexyl. 3.3.5-trimethylcyclohexyl, 2-(*o*-methoxyphenyl)ethyl, 2-(1,2.3,4-tetrahydronaphthyl), 4-phenylbutyl, 2-methyl-2-phenylbutyl, 2-(*m*-fluorophenyl)ethyl, 2-(*p*-fluorophenyl)ethyl, 2-(3-hydroxy-3-phenyl)propyl, (S)-2-hydroxy-2-phenylethyl, (R)-2-hydroxy-2-phenylethyl, 2-(3-*m*-chlorophenyl-2-methyl)propyl, 2-(3-*p*-chlorophenyl-2-methyl)propyl, 4-*tert*-butyl-cyclohexyl, (S)-1-(cyclohexyl)ethyl. 2-(3-(3,4-dimethylphenyl)-2-methyl)propyl, 3,3-dimethylbutyl, 2-(5-methyl)hexyl. 1-myrtanyl. 2-bornyl, 3-pinanemethyl, 2,2,3,3,4,4,5,5-octafluoropentyl. *p*-fluoro-α.α-dimethylphenethyl, 2-naphthyl. 2-bornanyl, cyclohexylmethyl, 3-methylcyclohexyl, 4-methylcyclohexyl, 3,4-dimethylcyclohexyl. 5-chloro-tricyclo[2.2.1]heptyl, *o*-α,α-dimethylphenethyl, 2-

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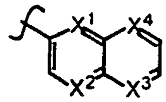
indanyl, 2-spiro[4.5]decyl, 2-phenylethyl, 1-adamantylethyl, 1-(1-bicyclo[2.2.1]hept-2-yl)ethyl, 2-(2-methyl-2-phenylpropyl), 2-(*o*-fluorophenyl)ethyl, 1-(cyclohexyl)ethyl, and cyclohexyl.

In a still further embodiment of the invention, Ar comprises a group having the formula



where X^1, X^2, X^3, and X^4 independently can be N or CH, provided that not more than two of X^1, X^2, X^3, and X^4 can be N. In a preferred embodiment, X^1 is N, and/or X^2 is N. In another embodiment, X^3 is N. In still another embodiment, X^1 is CH and X^2 is N.

In yet another embodiment, Ar is an optionally substituted 2-, 3-, or 4-pyridyl moiety, or Ar is a 6-benzothiazolyl moiety. The compound is selected from the group consisting of *N*-[6-(2-Methylquinolyl)]-1-adamantanecarboxamide, *N*-(6-Quinolyl)-1-adamantanecarboxamide, *N*-(2-Quinolyl)-1-adamantanecarboxamide, *N*-(3-Quinolyl)-1-adamantane-carboxamide, 6-Quinolyl-1-adamantanecarboxylate, 1-Adamantyl-6-quinolinecarboxylate, 2,2,3,3,4,4,5,5-Octafluoro-1-pentyl-6-quinolinecarboxylate, 1-Adamantanemethyl-6-quinolinecarboxylate, 1-Adamantyl-2-quinoxalinecarboxylate, *N*-(1-Adamantyl)-3-quinoline-carboxamide, *N*-(1-Adamantyl)-2-quinolinecarboxamide, *N*-(2-Adamantyl)-2-quinoxalinecarboxamide, *N*-[(1R,2R,3R,5S)-3-Pinanemethyl]-2-quinoxaline-carboxamide, *N*-(1-Adamantyl)-2-quinoxalinecarboxamide, *N*-(1-Adamantyl)-6-quinolinecarboxamide, *N*-(*exo*-2-Norbornanyl)-2-quinoxalinecarboxamide, *N*-[(1R,2S,4S)-Bornyl]-2-quinoxalinecarboxamide, *N*-(3-Noradamantyl)-2-quinoxalinecarboxamide, *N*-[(1R,2R,3R,5S)Iso-pinocamphenyl]-2-quinoxalinecarboxamide, *N*-[(1S,2S,3S,5R)-Isopinocamphenyl]-2-quinoxaline-carboxamide, *N*-(5-Chloro-[2.2.1.0]tricyclo-2,6-hepta-3-yl)-2-quinoxalinecarboxamide, *N*-([4.3.1.1)Tricyclo-3,8-undeca-3-yl)-2-quinoxalinecarboxamide, *N*-[(1S,2R,5S)-*cis*-Myrtanyl]-2-quinoxalinecarboxamide, *N*-[(1R,2R,4S)Isobornyl]-2-quinoxalinecarboxamide,

N-[endo-(±)-2-Norbornanyl]-2-quinoxalinecarboxamide. N-[(R)-2-Phenyl-1 propyl]-2-quinoxalinecarboxamide. N-[(S)-2-Phenyl-1-propyl]-2-quinoxalinecarboxamide. N-(2-Indanyl)-2-quinoxalinecarboxamide. 1-Adamantanemethyl 6-quinolyl ether. 1-Adamantyl-3-quinolinecarboxylate. N-(α,α-Dimethylphenethyl)-2-quinoxalinecarboxamide. N-(α,α-Dimethyl-2-chlorophenethyl)-2-quinoxalinecarboxamide. N-(α,α-Dimethyl-4-fluorophenethyl)-2-quinoxalinecarboxamide. N-(β-Methylphenethyl)-2-quinoxalinecarboxamide, N-(3-Methylcyclohexyl)-2-quinoxalinecarboxamide, N-(2,3-Dimethylcyclohexyl)-2-quinoxalinecarboxamide, N-[(1S,2S,3S,SR)-3-Pinanemethyl]-2-quinoxaline-carboxamide, N-(1-Adamantanemethyl)-2-quinoxaline-carboxamide. N-(4-Methylcyclohexyl)-2-quinoxaline-carboxamide. N-[(1S,2S,5S)-*trans*-Myrtanyl]-2-quinoxaline-carboxamide, and N-[(1R,2R,5R)-*trans*-Myrtanyl]-2-quinoxalinecarboxamide. and pharmaceutically acceptable salts thereof.

In a preferred embodiment, the compound is selected from the group consisting of N-(1-Adamantyl)-3-quinolinecarboxamide. N-(1-Adamantyl)-2-quinolinecarboxamide. N-(2-Adamantyl)-2-quinoxaline-carboxamide. N-[(1R,2R,3R,5S)-3-Pinanemethyl]-2-quinoxaline-carboxamide. N-(1-Adamantyl)-2-quinoxaline-carboxamide. N-(1-Adamantyl)-6-quinolinecarboxamide. N-(*exo*-2-Norbornanyl)-2-quinoxaline-carboxamide. N-[(1R,2S,4S)-Bornyl]-2-quinoxaline-carboxamide. N-(3-Noradamantyl)-2-quinoxaline-carboxamide. N-[(1R,2R,3R,5S)-Isopinocamphenyl]-2-quinoxaline-carboxamide. N-[(1S,2S,3S,5R)-Isopinocamphenyl]-2-quinoxaline-carboxamide. N-(5-Chloro-[2.2.1.0]tricyclo-2,6-hepta-3-yl)-2-quinoxaline-carboxamide. N-([4.3.1.1]Tricyclo-3,8-undeca-3-yl)-2-quinoxaline-carboxamide. N-[(1S,2R,5S)-*cis*-Myrtanyl]-2-quinoxaline-carboxamide. N-[(1R,2R,4S)Isobornyl)-2-quinoxaline-carboxamide, N-[*endo*-(±)-2-Norbornanyl]-2-quinoxaline-carboxamide, N-[(1S,2S,3S,5R)-3-Pinanemethyl]-2-quinoxalinecarboxamide. N-(1-Adamantanemethyl)-2-quinoxalinecarboxamide, N-[(1S,2S,5S)-*trans*-Myrtanyl]-2-quinoxalinecarboxamide, and N-[(1R,2R,5R)-*trans*-Myrtanyl]-2-quinoxalinecarboxamide. and pharmaceutically acceptable salts thereof.

In another embodiment, the compound is selected from the group consisting of N-[6-(2-Methylquinolyl)]-1-adamantanecarboxamide. N-(6-Quinolyl)-1-adamantane-carboxamide. N-(2-Quinolyl)-1-adamantanecarboxamide.

and *N*-(3-Quinolyl)-1-adamantanecarboxamide. *N*-(3-Methylcyclohexyl)-2-quinoxalinecarboxamide. *N*-(2,3-Dimethylcyclohexyl)-2-quinoxalinecarboxamide. *N*-[(1S,2S,3S,5R)-3-Pinanemethyl]-2-quinoxalinecarboxamide. *N*-(1-Adamantanemethyl)-2-quinoxalinecarboxamide, and *N*-(4-Methylcyclohexyl)-2-quinoxalinecarboxamide. *N*-[(R)-2-Phenyl-1-propyl-2-quinoxalinecarboxamide. *N*-[(S)-2-Phenyl-1-propyl]-2-quinoxalinecarboxamide. *N*-(2-Indanyl)-2-quinoxalinecarboxanride. *N*-(α-α-Dimethylphenethyl)-2-quinoxalinecarboxamide. *N*-(α,α-Dimethyl-2-chlorophenethyl)-2-quinoxalinecarboxamide. *N*-(α,α-Dimethyl-4-fluorophenethyl)-2-quinoxaline-carboxamide, and *N*-(β-Methylphenethyl)-2-quinoxaline-carboxamide. 1-Adamantanemethyl 6-quinolyl ether. 6-Quinolyl-1-adamantanecarboxylate. 1-Adamantyl-6-quinolinecarboxylate. 2,2,3,3,4,4,5,5-Octafluoro-1-pentyl 6-quinolinecarboxylate. 1-Adamantanemethyl 6-quinolinecarboxylate. 1-Adamantyl-2-quinoxalinecarboxylate, and 1-Adamantyl-3-quinolinecarboxylate, and pharmaceutically acceptable salts thereof.

In yet another embodiment, the compound is selected from the group consisting of 3-(1-Adamantanemethoxy)-2-chloroquinoxaline, 2-(1-Adamantanemethoxy)-3-methylquinoxaline, 3-(1-Adamantanemethoxy)-2-fluoroquinoxaline. 2-(1-Adamantanemethoxy)-3-trifluoromethylquinoxaline. *N*-[2-(4-Phenylthiazolyl)]-1-adamantanecarboxamide, *N*-[2-(5-Methyl-4-phenylthiazolyl)]-1-adamantanecarboxamide. 1-(1-Adamantyl)-2-(benzothiazol-2-ylsulfanyl)ethanone. *N*-(1-Adamantyl)-2-chloroquinoxaline-3-carboxamide. *N*-(1-Adamantyl)-3-methylquinoxaline-2-carboxamide, and *N*-(1-Adamantyl)-1-oxyquinoxaline-3-carboxamide. 4-Chlorophenyl 3-coumarincarboxylate. 2-(1-Adamantanemethylsulfanyl)quinoxaline, 3-(1-Adamantanemethoxy)-2-chloropyrazine. 1-(1-Adamantyl)-2-(4, 6-dimethylpyrimidin-2-ylsulfanyl)ethanone. 1-(1-Adamantyl)-2-(2-anisylsulfanyl)ethanone. 3-(1-Adamantanemethoxy)-1*H*-quinoxalin-2-one, 1-(1-Adamantyl)-2-(3-anisylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(4-anisylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(4-chlorophenylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(2-naphthylsulfanyl)ethanone, *N*-(2-[6-(1-Piperidinyl)pyrazinyl])-1-adamantanecarboxamide. *N*-(2-[6-(1-Piperidinyl)pyrazinyl])adamantan-1-ylmethylcarboxamide. 1-(1-Adamantyl)-2-(1-naphthylsulfanyl)ethanone. 1-(1-Adamantyl)-2-(8-quinolylsulfanyl)ethanone hydrochloride. 1-(1-Adamantyl)-2-(4-

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trifluoromethoxyphenoxy)ethanone, 2-(1-Adamantanemethoxy)quinoxaline, *N*-(*trans*-4-Methylcyclohexyl)-2-quinoxalinecarboxamide, *N*-(*cis*-4-Methylcyclohexyl)-2-quinoxalinecarboxamide, *N*-(*trans*-4-Methylcyclohexyl)-2-quinolinecarboxamide, *N*-(*trans*-4-Methylcyclohexyl)-3-quinolinecarboxamide, and *N*-(*trans*-4-Methylcyclohexyl)-6-quinolinecarboxamide, 2-(1-Adamantanemethylsulfinyl)-benzothiazole, *N*-(4-Phenylbutyl)-2-quinoxalinecarboxamide, 1-(1-Adamantyl)-2-(4, 6-dimethylpyrimidin-2-ylsulfanyl)ethanol, 1-(1-Adamantyl)-2-(3-chloroquinoxal-2-yl)ethanone, 2-(1-Adamantanemethylsulfanyl)-3-methylquinoxaline, *N*-(1-Adamantyl)-2-anisamide, *N*-(1-Adamantanemethyl)-2-anisamide, 1-(1-Adamantyl)-2-(4-chlorophenylsulfanyl)ethanone, 2-(1-Adamantanemethylsulfonyl)-3-methylquinoxaline, 1-(1-Adamantyl)-2-(4-fluorophenylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(3-fluorophenylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(2-methoxyphenoxy)ethanone, 1-(4-Anisylsulfanyl)butan-2-one, 1-(1-Adamantyl)-2-(4-anisidinyl)ethanone hydrochloride, 3, 3-Dimethyl-1-(4-anisylsulfanyl)butan-2-one, 1-(4-Biphenyl)-2-(4-anisylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(2-trifluoromethoxyphenylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(3-methylquinoxal-2-ylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(2-anisidinyl)ethanone hydrochloride, 1-(1-Adamantyl)-2-(4-trifluoromethoxyphenylamino)ethanone hydrochloride, 1-(1-Adamantyl)-2-(*N*-methyl-4-anisidinyl)ethanone hydrochloride, *N*-(1-Adamantyl)-7-trifluoromethylquinoline-3-carboxamide, *N*-(1-Adamantyl)-2-(1-piperizinyl)quinoxaline-3-carboxamide, *N*-(1-Adamantyl)-2-(2-aminoethylamino)quinoxaline-3-carboxamide, Methyl *N*-(3-quinolyl)-3-carboxyadamantane-1-carboxamide, 1-(1-Adamantyl)-2-[(*R*)-1-(1-naphthyl)ethan-1-ylamino]ethanone, *N*-(1-Adamantyl)-2-methoxyquinoxaline-3-carboxamide, Ethyl *N*-(1-adamantyl)-2-(3-propanoylamino)quinoxaline-3-carboxamide, *N*-(4-Chlorophenyl)-2, 3-dimethylquinoxaline-6-carboxamide, *N*-(1-Adamantyl)-6, 7-dimethylquinoxaline-2-carboxamide, *N*-((*S*)-1-Tetralinyl)-2-quinoxalinecarboxamide, *N*-(4-Chlorophenethyl)-2-quinoxalinecarboxamide, *N*-(6-Quinolyl)-2-quinoxalinecarboxamide, *N*-(1-Tetralinmethyl)-2-quinoxalinecarboxamide, *N*-(1-Indanmethyl)-2-quinoxalinecarboxamide, *N*-(4, 4-Dimethylcyclohexyl)-2-quinoxalinecarboxamide, and pharmaceutically acceptable salts thereof.

In accordance with another embodiment of the invention, there has been provided a pharmaceutical composition comprising a compound as set forth above, together with a pharmaceutically acceptable diluent or excipient.

In accordance with still another embodiment of the invention, there has been provided a method of making a compound as set forth above, comprising reacting a compound containing an activated carboxylic acid group with a compound containing an amine, hydroxyl, or thiol group.

In accordance with a still further embodiment of the invention, there has been provided a method of inhibiting activation of an mGluR Group I receptor, comprising treating a cell containing said mGluR Group I receptor with an effective amount of a compound as set forth above.

In yet another embodiment of the invention, there has been provided a method of inhibiting neuronal damage caused by excitatory activation of an mGluR Group I receptor, comprising treating neurons with an effective amount of a compound as set forth above.

In accordance with a further embodiment of the invention, there has been provided a method of treating a disease associated with glutamate-induced neuronal damage, comprising administering to a patient suffering from said disease an effective amount of a composition as set forth above.

Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows illustrative compounds of the invention.

DETAILED DESCRIPTION

The invention provides compounds that are potent and selective antagonists of Group I metabotropic glutamate receptors. The compounds contemplated by the invention can be represented by the general formula I:

$$R - [\text{Linker}] - Ar$$

where R is a straight or branched chain alkyl, arylalkyl, or optionally substituted alicyclic group, and Ar is an optionally substituted aromatic, heteroaromatic, arylalkyl, or heteroaralkyl moiety. The [linker] moiety is a group that not only covalently binds to the Ar and R moieties, but also facilitates adoption of the correct spatial orientation by Ar and R to allow receptor binding.

Structure of the Ar moiety

The Ar moiety generally may contain up to ten carbon atoms, although the skilled artisan will recognize that Ar groups with more than ten carbon atoms are within the scope of the invention. Ar can be a monocyclic or fused bicyclic aryl, alkaryl, heteroaryl or heteroarylalkyl group. The ring systems encompassed by Ar can contain up to four heteroatoms, independently selected from the group consisting of N, S, and O. When Ar is a heteroaryl ring or ring system, it preferably contains one or two heteroatoms. At least one of the heteroatoms preferably is N.

Monocyclic Ar groups include, but are not limited to: phenyl, thiazoyl, furyl, pyranyl, 2H-pyrrolyl, thienyl, pyrroyl, imidazoyl, pyrazoyl, pyridyl, pyrazinyl, pyrimidinyl, and pyridazinyl moieties. Fused bicyclic Ar groups include, but are not limited to: benzothiazole, benzimidazole, 3H-indolyl, indolyl, indazoyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalizinyl, naphthyridinyl, quinazolinyl, cinnolinyl, isothiazolyl, quinoxalinyl indolizinyl, isoindolyl, benzothienyl, benzofuranyl, isobenzofuranyl, and chromenyl moieties. Ar preferably is a quinoxalinyl, quinolinyl, or pyridyl moiety.

Other Ar moieties include the 3,4-methylenedioxy and 3,4-dioxane rings. The Ar moiety optionally may independently be substituted with up to two C_1-C_3

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alkyl groups, or up to two halogen atoms, where halogen is selected from F, Cl, Br, and I.

Structure of the R moiety

The R moiety generally may contain between four and eleven carbon atoms, although the skilled artisan will recognize that R moieties with 12, 13, 14, 15, or 16 carbon atoms will be possible. Although R can contain 4, 5 or 6 carbon atoms, preferably R contains at least 7 carbon atoms. Preferably, R is optionally substituted alkyl, cycloalkyl, cycloalkylmethyl, or optionally substituted phenylalkyl. Generally, some or all of the hydrogen atoms on up to two methine, methylene, or methyl groups of R may be replaced by substituents independently selected from the group consisting of F, Cl, OH, OMe, =O, and -COOH groups. However, more than two hydrogen atoms may be replaced with fluorine, and R may be perfluorinated.

Exemplary R moieties include, but are not limited to: adamantyl, 2-adamantyl, (1S,2S,3S,5R)-isopinocamphenyl, tricyclo[4.3.1.1(3,8)]undec-3-yl, (1S,2R,5S)-*cis*-myrtanyl, (1R,2R,4S)-isobornyl, (1R,2R,3R,5S)-isopinocamphenyl (1S,2S,5S)-trans-myrtanyl (1R,2R,5R)-trans-myrtanyl, (1R,2S,4S)-bornyl, 1-adamantanemethyl, 3-noradamantyl (1S,2S,3S,5R)-3-pinanemethyl, cyclooctyl, dimethylphenethyl, (S)-2-phenyl-1-propyl, cycloheptyl, and 4-methyl-2-hexyl groups. Each of these exemplary R moieties may also be substituted in the manner set forth above.

Other preferred R groups include 2,2,3,3,4,4,4-heptafluorobutyl, 4-ketoadamantyl, 3-phenyl-2-methylpropyl, 3,5-dimethyladamantyl, *trans*-2-phenylcyclopropyl, 2-methylcyclohexyl, 3,3,5-trimethylcyclohexyl, 2-(*o*-methoxyphenyl)ethyl, 2-(1,2,3,4-tetrahydronaphthyl), 4-phenylbutyl, 2-methyl-2-phenylbutyl, 2-(*m*-fluorophenyl)ethyl, 2-(p-fluorophenyl)ethyl, 2-(3-hydroxy-3-phenyl)propyl, (S)-2-hydroxy-2-phenylethyl, (R)-2-hydroxy-2-phenylethyl, 2-(3-*m*-chlorophenyl-2-methyl)propyl, 2-(3-*p*-chlorophenyl-2-methyl)propyl, 4-*tert*-butyl-cyclohexyl, (S)-1-(cyclohexyl)ethyl, 2-(3-(3,4-dimethylphenyl)-2-methyl)propyl, 3,3-dimethylbutyl, 2-(5-methyl)hexyl, 1-myrtanyl, 2-bornyl, 3-pinanemethyl, 2,2,3,3,4,4,5,5-octafluoropentyl, *p*-fluoro- 2,2 -dimethylphenethyl, 2-naphthyl, 2-bornanyl, cyclohexylmethyl, 3-methylcyclohexyl, 4-methylcyclohexyl, 3,4-dimethylcyclohexyl, 5-chloro-

tricyclo[2.2.1]heptyl. *o*- . -dimethylphenethyl. 2-indanyl. 2-spiro[4.5]decyl. 2-phenylethyl. 1-adamantylethyl. 1-(1-bicyclo[2.2.1]hept-2-yl)ethyl. 2-(2-methyl-2-phenylpropyl), 2-(*o*-fluorophenyl)ethyl, 1-(cyclohexyl)ethyl, cyclohexyl, butan-2-onyl, diphenylene, 3-carboxyladamantyl, 1-tetrahydronaphthelenyl, 1-indanyl, 4-methylcyclohexyl, and 4.4-dimethylcyclohexyl moieties. Again. each of these exemplary R moieties may be substituted in the manner set forth above. When compounds may be present in alternative isomeric configurations, for example, *trans* or *cis*-4-methylcyclohexyl, the R moiety may have any of the possible configurations. Similarly, if a compound exists as enantiomers. the R moiety can be either of the enantiomers, or may be a racemate.

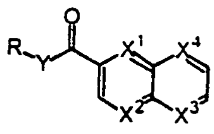
Structure of the [linker] moiety

The [linker] moiety generally has the structure $-(CH_2)_n-$, where n is 2-6. Up to four CH_2 groups may independently be replaced with groups selected from the group consisting of a C_1-C_3 alkyl group, CHOH. CO, O, S. SO. SO2. N. NH, and NO, provided that two heteroatoms may not be adjacent except when those atoms are both N (forming an -N=N- linkage) or are both NH (forming an -NH-NH- linkage). Any two adjacent CH_2 groups also may be replaced by an alkene or alkyne group.

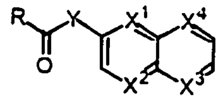
In a preferred embodiment, [linker] comprises an amide. ester. thioester. ketomethylene. ether. alkylether, ethylene. ethenyl. acetylenyl. hydroxyalkyl. alkylsulfone. or alkyl alkylsulfoxide group. Preferably, [linker] is an $-O-(CH_2)_m-$, $-CO-Y-(CH_2)_m-$, or $-S(O)_n-(CH_2)_m-$ group, where Y is CH_2. NH, O. or S. and m is 1-4, and n is 0-2. The [linker] moiety may have either one of two possible orientations with respect to the R and Ar groups. Thus, for example. the invention encompasses compounds having the configuration $R-O-(CH_2)_m-Ar$ and $R-(CH_2)_m-O-R$.

Design and synthesis of mGluR Group I antagonists

In one embodiment, compounds according to the invention are esters and amides of monocyclic or fused bicyclic aromatic and heteroaromatic carboxylic acids. phenols and amines. In a preferred embodiment. the compounds may be represented by the Formulae II or III:

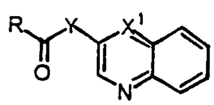


II

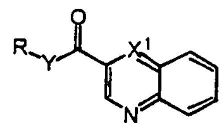


III

In Formulae II and III, Y can be either O, S, NH, or CH_2; and X^1, X^2, X^3, and X^4 independently can be N or CH. Preferably, one or two of X^1, X^2, X^3, and X^4 are N, and the remainder are CH. Preferred compounds contemplated by the invention have the formula IV or V, where R, Y and X^1 are as defined above.

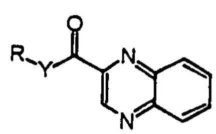


IV

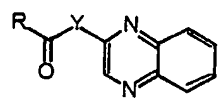


V

In another preferred embodiment of the invention, the compounds have the Formulae VI or VII :



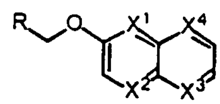
VI



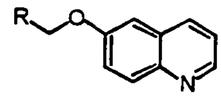
VII

where R and Y are as defined above. In a first embodiment of the compounds of Formula VI, Y is N, R is an unsubstituted or monosubstituted 1,1,-dimethylphenylethylamine or 1,1-dimethylbenzylamine moiety, where the substitutuent preferably is an *o*-, *m*-, or *p*-chlorine or *p*-methoxy group. In a second embodiment of the compounds of Formula VI, Y is N, and R is an *o*-, *m*-, or *p*-methoxy substituted phenylethylamine. Compounds of the first and second embodiments appear to exhibit selectivity for the $mGluR_1$ receptor. In a third embodiment, of the compounds of Formula VI, Y is N, and R is an *o*, *m*, or *p*-fluoro-substituted phenylethylamine. Compounds of the third embodiment appear not to discriminate between the $mGluR_1$ and $mGluR_5$ receptor subtypes.

In yet another preferred embodiment of the invention, the compounds have the Formulae VIII or IX:



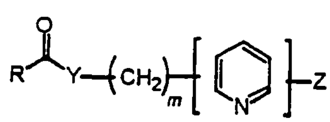
VIII



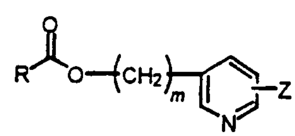
IX

wherein X^{1-4} and R are as defined above. In a first embodiment of compounds of Formula VIII, X^1 and X^2 are N, X^3 and X^4 are H, R is 1-adamantyl, and a substituent is present on the carbon atom ortho to both the linker and X^2. The substituent preferably is a halogen, such as chlorine, or an alkyl group, such as methyl. In a second embodiment of compound IX, R is 1-adamantyl. Compounds of these first and second embodiments appear to exhibit selectivity for the $mGluR_1$ receptor.

In still another embodiment, the compounds may have the Formulae X or XI, where Z is a pharmaceutically acceptable substituent. The skilled artisan will recognize that pharmaceutically acceptable Z groups are those groups that do not deleteriously reduce the receptor binding activity of the compound. Suitable Z groups include, but are not limited to halogen, lower alkyl, oxygen or amine, and their pharmaceutically acceptable derivatives including ethers, esters, and amides. Preferably, Z contains 0-4 carbon atoms.



X



XI

In each of the compounds described above, "alkyl" denotes both straight and branched chain alkyl. In other embodiments, R is adamantyl, the linker is -CO-CH_2-S-, and Ar is *m*- or *o*-alkyloxyphenyl, or 3,4-methylenedioxy or 3,4-dioxane.

In general, it appears that selective antagonism of the $mGluR_1$ receptor can be attained with compounds of the formula R-CO-N-Ar_1, where Ar_1 is an

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aromatic or heteroaromatic group such as a quinolinyl. quinoxalinyl. thiazolidinyl, phenyl. benzimidazoyl, or pyridyl group.

The skilled artisan also will recognize that the compounds of the invention encompass salts of the compounds described above. These salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts or optionally alkylated ammonium salts, such as hydrochloric. hydrobromic. hydroiodic, phosphoric, sulfuric. trifluoroacetic. malonic, succinic. citric. mandelic, benzoic, cinnamic, methanesulfonic and similar ones, and include acids related to the pharmaceutically acceptable salts listed in the *Journal of Pharmaceutical Sciences*. 66:2 (1977) and incorporated herein by reference.

Examples of compounds according to the present invention are set forth in Table 1 below.

Preparation of mGluR Group I antagonists

The skilled artisan will recognize that mGluR Group I antagonists according to the invention may be prepared by methods that are well known in the art, using widely recognized techniques of organic chemistry. Suitable reactions are described in standard textbooks of organic chemistry. For example. see March, Advanced Organic Chemistry, 2d ed., McGraw Hill (1977).

For example, the compounds generally may be prepared by formation of the [linker] moiety between two precursor compounds containing suitable Ar and R moieties. When the linker contains an amide linkage, the amide may be formed using well known techniques. such as reaction between an amine and an acid chloride, or by reaction in the presence of a coupling reagent such as carbonyldiimidazole, or a carbodiimide such as, for example, 1,3-dicyclohexylcarbodiimide (DCC). Formation of ester and thioester linkages can be achieved in similar fashion.

When the [linker] moiety contains an ether linkage, the ether function also can be prepared using standard techniques. For example, ethers can be formed using the Mitsunobu reaction, where a primary alcohol function is displaced by another hydroxy group via activation using PPh_3 and diethylazodicarboxylate (DEAD). Thioether linkages may be prepared by displacement of a leaving group such as halide with a thiolate anion, generated by deprotonation of a thiol group with base.

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When the [linker] moiety contains a ketomethylene group, it can be formed by alkylation of a ketone enolate. Thus, for example, a methyl ketone can be deprotonated using a strong base such as lithium diisopropylamide (LDA), followed by reaction with an alkyl halide. Alternatively, a ketomethylene function can be prepared via addition of an organometallic compound, such as a Grignard reagent, to an aldehyde, followed by oxidation of the resultant hydroxyl group to a ketone. Suitable reagents for oxidizing alcohols to ketones are well known in the art.

[Linker] moieties containing other heteroatom groups also may be prepared using methods that are well known in the art. *N,N'*-Disubstituted hydrazine compounds may be prepared via reductive amination of hydrazones formed by reaction of a monosubstituted hydrazone with an aldehyde. *N,N'*-Disubstituted azo compounds can be formed, for example, by oxidation of the corresponding hydrazines.

In most cases, the precursor Ar and R moieties are readily available, or may be prepared using straightforward techniques of organic chemistry. Many compounds are commercially available, for example, from Aldrich Chemical Company, Milwaukee, WI. When the compounds are not commercially available, they may readily prepared from available precursors using straightforward transformations that are well known in the art.

For example, carboxylic acids may be converted into the corresponding acid chlorides by reaction with, for example, thionyl chloride or oxalyl chloride. An example of such a reaction is provided below in Example 3. Compounds containing a hydroxy function may be converted into the corresponding amine by (i) conversion of the hydroxyl group into a leaving group, such as a sulfonic acid ester (such as a triflate, mesylate, or tosylate) or a halide, (ii) displacement with azide ion, and (iii) reduction of the resulting azide by, for example, hydrogenation over a platinum oxide catalyst. An illustration of such a transformation is provided below in Example 12.

Testing of compounds for mGluR Group I antagonist activity

The pharmacological properties of the compounds of the invention can be analyzed using standard assays for functional activity. Examples of glutamate receptor assays are well known in the art, for example, see Aramori *et al.*,

Neuron 8:757 (1992); Tanabe *et* al., *Neuron* 8:169 (1992). The methodology described in those publications is incorporated herein by reference.

Conveniently, the compounds of the invention may be studied using an assay that measures inhibition of intracellular calcium mobilization in cells expressing recombinant receptors that can bind the compounds. Suitable receptor constructs are well known in the art and are also described, for example, in WO 97/05252, the contents of which are hereby incorporated by reference in their entirety.

Thus, HEK-293 cells (human embryonic kidney cells, available from the American Type Culture Collection, Rockville, MD, Accession Number CRL 1573) are stably transfected with a DNA construct expressing a recombinant receptor. The stably transfected cells are cultured in high glucose DMEM (Gibco 092) containing 0.8 mM glutamine, 10% FBS, and 200 μM hygromycin B.

A protocol for measuring intracellular calcium mobilization in response to changes in extracellular calcium using the calcium-sensitive dye Fura has been described previously. Briefly, HEK-293 cells, stably transfected with a DNA construct encoding a recombinant receptor, are loaded with Fura dye. The cells then are washed, resuspended, and maintained at 37 °C. The cells are diluted into cuvettes for recording fluorescent signals. Measurements of fluorescence are performed at 37 °C using standard methods, and concentrations of intracellular Ca^{2+} are calculated using a dissociation constant (Kd) of 224 nM and applying equation:

$$[Ca^{2+}]_i = (F - F_{min} / F_{max}) \times Kd$$

where F is fluorescence at any particular time of interest, F_{min} is determined by chelating all calcium available, therefore, no fura 2 is bound to calcium, and F_{max} is determined by fully saturating all the fura 2 available with calcium.

A detailed protocol for testing the compounds of the invention is provided below at Example 15.

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Preparation of pharmaceutical compositions containing mGluR antagonists, and their use in treating neurological disorders

The compounds of the invention are useful for treating neurological disorders or diseases. While these compounds will typically be used in therapy for human patients, they may also be used in veterinary medicine to treat similar or identical diseases.

In therapeutic and/or diagnostic applications, the compounds of the invention can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in Remington's Pharmaceutical Sciences: Drug Receptors and Receptor Theory, 18th ed., Mack Publishing Co. (1990).

The compounds according to the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.01 to about 1000 mg, preferably from about 0.5 to about 100 mg, per day may be used. A most preferable dosage is about 2 mg to about 70 mg per day. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

Pharmaceutically acceptable salts are generally well known to those of ordinary skill in the art, and may include, by way of example but not limitation, acetate, benzenesulfonate, besylate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/disphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, or teoclate. Other pharmaceutically acceptable salts may be found in, for example, Remington's Pharmaceutical Sciences: (18th ed.), Mack Publishing Co., Easton.PA (1990).

Preferred pharmaceutically acceptable salts include, for example, acetate, benzoate, bromide, carbonate, citrate, gluconate, hydrobromide, hydrochloride,

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maleate, mesylate, napsylate, pamoate (embonate), phosphate, salicylate, succinate, sulfate, or tartrate.

Depending on the specific conditions being treated, such agents may be formulated into liquid or solid dosage forms and administered systemically or locally. The agents may be delivered, for example, in a timed- or sustained-release form as is known to those skilled in the art. Techniques for formulation and administration may be found in Remington's Pharmaceutical Sciences; (18th ed.), Mack Publishing Co., Easton, PA (1990). Suitable routes may include oral, buccal, sublingual, rectal, transdermal, vaginal, transmucosal, nasal or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections, just to name a few.

For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

Use of pharmaceutically acceptable carriers to formulate the compounds herein disclosed for the practice of the invention into dosages suitable for systemic administration is within the scope of the invention. With proper choice of carrier and suitable manufacturing practice, the compositions of the present invention, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions.

Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethyl-cellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers may be added.

The present invention, thus generally described, will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

EXAMPLES

General Experimental Methods

Capillary gas chromatographic and mass spectral data were obtained using a Hewlett-Packard (HP) 5890 Series II Gas Chromatograph coupled to an HP 5971 Series Mass Selective Detector [Ultra-2 Ultra Performance Capillary Column (crosslinked 5% PhMe silicone); column length, 25 m; column i.d., 0.20 mm; helium flow rate, 60 mL/min; injector temp., 250 °C; temperature program, 20 C/min from 125 to 325 °C for 10 min, then held constant at 325 °C for 6 min]. Thin-layer chromatography was performed using Analtech Uniplate 250-μm silica gel HF TLC plates. UV light sometimes in conjunction with ninhydrin and Dragendorff's spray reagents (Sigma Chemical Co.) were used for detecting compounds on the TLC plates. Reagents used in reactions were purchased from the Aldrich Chemical Co. (Milwaukee, WI), Sigma Chemical Co. (Saint Louis, MO), Fluka Chemical Corp. (Milwaukee, WI), Fisher Scientific (Pittsburgh, PA), TCI America (Portland, OR), or Lancaster Synthesis (Windham, NH).

EXAMPLE 1: Preparation of *N*-[6-(2-Methylquinolyl)]-1-adamantanecarboxamide (40)

2-Methyl-6-aminoquinoline

A mixture of 2-methyl-6-nitroquinoline (1.00 g, 5.31 mmol) and Pearlman's catalyst [palladium dihydroxide on activated charcoal (~20% palladium); 0.10 g] in ethyl acetate (40 mL) was stirred under hydrogen gas (1 atm) at 60°C for 1.5 h. The reaction mixture was filtered and the filtrate was rotary evaporated. This provided 0.81 g (96%) of 2-methyl-6-aminoquinoline as a yellow solid.

N-[6-(2-Methylquinolyl)]-1-adamantanecarboxamide (40)

1-Adamantanecarbonyl chloride (1.02 g, 5.13 mmol) in pyridine (2 mL) was added to a solution of 2-methyl-6-aminoquinoline (0.81 g, 5.1 mmol) in pyridine (8 mL). The reaction was stirred for 17 h. To the stirring reaction mixture was added water (100 mL) which caused the product to precipitate.. This precipitate was filtered and then washed with water (3 x 25 mL) and diethyl ether (3 x 25 mL). This provided 1.07 g (65%) of (40) as a cream-colored powder:

rt=13.49 min.: m/z (rel. int.) 320 (M+,30), 235 (8), 158 (4), 157 (6), 136 (11), 135 (100), 130 (11), 107 (7), 93 (15), 91 (8), 79 (18), 77 (11), 67 (6).

In a similar manner, the following *N*-quinolyl-1-adamantanecarboxamides were prepared:

N-(6-Quinolyl)-1-adamantanecarboxamide (18)

Prepared from 1-adamantanecarbonyl chloride (1.37 g, 6.90 mmol), 6-aminoquinoline (0.59 g, 4.1 mmol), pyridine (20 mL), and water (200 mL) yielding 1.25 g (100%) of (18):

rt=13.24 min.;m/z (rel. int.) 306 (M+,23), 221 (6), 144 (3), 136 (12), 135 (100), 116 (10), 107 (7), 93 (15), 91 (8), 79 (18), 77 (9), 67 (7), 41 (6).

N-(2-Quinolyl)-1-adamantanecarboxamide hydrochloride (81)

Prepared from 1-adamantanecarbonyl chloride (0.75 g, 3.8 mmol), 2-aminoquinoline (0.60 g, 4.2 mmol), pyridine (10 mL), and water (100 mL). Forming the hydrochloride salt with diethyl ethereal hydrogen chloride yielded 0.19 g (15%) of (81):

rt=12.24 min;m/z (rel. int.) 306 (M+,80), 305 (23), 277 (8), 263 (8), 221 (10), 172 (9), 171 (72), 145 (16), 144 (61), 143 (13), 136 (11), 135 (100), 128 (33), 117 (17), 116 (24), 107 (18), 105 (8), 101 (10), 93 (40), 91 (29), 89 (13), 81 (14), 79 (55), 77 (35), 67 (18), 65 (10), 55 (12), 53 (10), 41 (20).

N-(3-Quinolyl)-1-adamantanecarboxamide (86)

Prepared from 1-adamantanecarbonyl chloride (0.75 g, 3.8 mmol), 3-aminoquinoline (0.60 g, 4.2 mmol), pyridine (10 mL), and water (100 mL) yielding 0.33 g (29%) of (86):

rt=13.01 min.: m/z (rel. int.) 306 (M+,22), 136 (11), 135 (100), 116 (11), 107 (8), 93 (15), 91 (8), 89 (7), 79 (17), 77 (8), 67 (6), 65 (3).

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N-(*trans*-4-Methylcyclohexyl)-2-quinoxalinecarboxamide (299)

Using the method of Booth (J. Chem. Soc., 1958, 2688; J. Chem. Soc., 1971, 1047; Tetrahedron, 1967, 23, 2421), hydroxylamine (3.8 g, 55 mmol), ethanol (50 mL), pyridine (4.44 mL, 55 mmol), and 4-methyl cyclohexanone (6.1 mL, 50 mmol) were stirred at ambient temperature for 16 hours and then heated at reflux for 15 minutes. The ethanol was then removed in vacuo and the residual oil dissolved in ethylacetate (100 mL). The organic layer was washed with water (2X), brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to a clear oil (the oxime product), which crystallized upon standing.

Without further purification 1.9 g (15 mmol) of the intermediate oxime in absolute ethanol (40 mL) was heated to reflux and treated with (in small portions) sodium metal (4 g). The reaction was heated at reflux until the sodium was consumed. The reaction was cooled and treated with water (10 mL). The reaction was transferred into a flask containing ice and concentrated HCl (6 mL). The ethanol was removed in vacuo and the remaining aqueous phase washed with diethyl ether (3X, to remove unreduced oxime). The remaining aqueous phase was concentrated to afford 1.8 g of a white crystalline solid (the *trans*-4-methylcyclohexylamine hydrochloride product).

Without further purification 750 mg (5 mmol) of *trans*-4-methylcyclohexyl amine hydrochloride in dichloromethane (10 mL) was treated with pyridine (1.62 mL, 20 mmol) followed by the addition of 2-quinoxaloyl chloride (963 mg, 55 mmol). The reaction was stirred at ambient temperature for 16 hours and diluted with chloroform (25 mL). The organics were washed with 10% HCl (3X), 1 N NaOH (3X), brine, dried over anhydrous $MgSO_4$, filtered and concentrated to a solid. Chromatography (MPLC) of the crude reaction material through silica (7 x 4 cm i.d., BIOTAGE, KP-SIL, 60 angstroms) using ethylacetate-hexane (1:4) afforded 470 mg of the desired product, N-(*trans*-4-methylcyclohexyl)-2-quinoxalinecarboxamide. Thin-layer chromatography (TLC, silica) using ethylacetate-hexane (1:4) showed a single UV active component at R_f 0.19. GC/EI-MS gave m/z (rel. int.) 269 (M^+, 39), 212 (8), 198 (6), 174 (15), 157 (21), 129 (100), 112 (43), and 102 (46).

EXAMPLE 2: Preparation of 6-Quinolyl 1-adamantanecarboxylate (41)

1-Adamantanecarbonyl chloride (1.37 g, 6.90 mmol) in pyridine (5 mL) was added to a solution of 6-hydroxyquinoline (1.00 g, 6.89 mmol) in pyridine (15 mL). The reaction was stirred for 16 h. To the stirring reaction mixture was added water (200 mL) which caused the product to precipitate. This precipitate was filtered, washed with water (3 x 50 mL), and dried under high vacuum. This provided 1.56 g (73.7%) of (41) as a light-brown powder:

rt=11.41 min.; m/z (rel. int.) 307 (M+,2), 136 (11), 135 (100), 116 (11), 107 (7), 93 (14), 92 (2), 91 (8), 89 (7), 79 (16), 77 (8).

EXAMPLE 3: Preparation of 1-Adamantyl 6-quinolinecarboxylate (61)

6-Quinolinecarbonyl chloride hydrochloride

6-Quinolinecarboxylic acid was refluxed in thionyl chloride for 30 min. The excess thionyl chloride was then removed by rotary evaporation (90° C) to provide 6-quinolinecarbonyl chloride hydrochloride.

1-Adamantyl 6-quinolinecarboxylate (61)

6-Quinolinecarbonyl chloride hydrochloride (0.76g, 3.3 mmol) in pyridine (2 mL) was added to a solution of 1-adamantanol (0.60 g, 3.9 mmol) in pyridine (8 mL). The reaction was stirred at 70°C for 16 h. To the stirring reaction mixture was added water (100 mL) which caused the product to precipitate. This precipitate was filtered and then washed with water (3 x 25 mL). The filter cake was dissolved in ethanol (20 mL) and water was then added to the cloud point (16 mL). The crystallizing solution was allowed to stand for 15 h. Filtering and drying under high vacuum for 7 h provided 0.32 g (26%) of (61) as light brown needle-like crystals:

rt=11.48 min.; m/z (rel. int.) 307 (M+,99), 306 (92), 262 (15), 174 (12), 173 (13), 157 (10), 156 (88), 135 (81), 134 (33), 129 (13), 128 (100), 127 (10), 119 (11), 107 (18), 102 (16), 101 (37), 93 (51), 92 (76), 91 (35), 81 (14), 79 (55), 78 (15), 77 (49), 75 (17), 67 (24), 55 (18), 53 (13), 51 (13), 41 (31).

In a similar manner, the following alkyl 6-quinoline- and 2-quinoxalinecarboxylates were prepared:

2,2,3,3,4,4,5,5-Octafluoro-1-pentyl-6-quinoline-carboxylate hydrochloride (68)

Prepared from 6-quinolinecarbonyl chloride hydrochloride (0.75 g, 3.3 mmol), 2,2,3,3,4,4,5,5-octafluoro-1-pentanol (0.60 mL, 4.3 mmol), pyridine (10 mL), and water (100 mL). Forming the hydrochloride salt with ethereal hydrogen chloride yielded 0.88 g (69%) of (68):

rt=7.11 min.; m/z (rel. int.) 387 (M+,26), 156 (100), 129 (6), 128 (48), 102 (6), 101 (16), 77 (6), 76 (2), 75 (8), 50 (14).

1-Adamantanemethyl 6-quinolinecarboxylate (73)

Prepared from 6-quinolinecarbonyl chloride hydrochloride (0.80 g, 3.5 mmol), 1-adamantanemethanol (0.60 g, 3.6 mmol), pyridine (10 mL), and water (100 mL) yielding 0.75 g (65%) of (73):

rt=11.90 min.; (rel. int.) 321 (M+,35), 320 (12), 263 (15), 156 (30), 148 (23), 136 (11), 135 (100), 135 (100), 129 (9), 128 (52), 107 (15), 106 (7), 105 (9), 102 (7), 101 (16), 93 (34), 92 (20), 91 (20), 81 (11), 80 (7), 79 (40), 78 (6), 77 (24), 75 (7), 67 (14), 55 (9), 53 (6), 51 (6), 41 (14).

1-Adamantyl 2-quinoxalinecarboxylate (92)

Prepared from 2-quinoxaloyl chloride (0.84 g, 4.4 mmol), 1-adamantanol (0.60 g, 3.9 mmol), pyridine (10 mL), and water (100 mL) yielding 0.20 g (16%) of (92):

rt=11.21 min.; m/z (rel. int.) 308 (M+,26), 264 (6), 136 (11), 136 (11), 135 (100), 134 (5), 130 (11), 129 (25), 107 (12), 102 (19), 93 (24), 92 (9), 91 (11), 81 (7), 79 (26), 77 (12), 76 (6), 75 (7), 67 (10), 55 (7), 51 (6), 41 (11).

EXAMPLE 4: Preparation of *N*-(1-Adamantyl)-3-quinolinecarboxamide (72)

1,1'-Carbonyldiimidazole (161 mg, 1.00 mmol) in *N,N*-dimethylformamide (1 mL) was added in one portion to a suspension of 3-quinolinecarboxylic acid (173 mg, 1.00 mmol) in *N,N*-dimethylformamide (1 mL). The resulting reaction solution was stirred for 2.5 h. 1-Adamantanamine (151 mg, 1.00 mmol) in *N,N*-dimethylformamide (0.5 mL) was added in one portion. The reaction mixture was stirred at 60 °C for 2 h. The reaction was then diluted with chloroform and washed with water (3 x 30 mL). The organic layer was dried (anhydrous magnesium sulfate), filtered through

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silica gel, and rotary evaporated. This provided 73 mg (24%) of (72) as a crystalline solid:

rt=11.02 min.: m/z (rel. int.) 306 (M+,78), 305 (42), 250 (19), 249 (100), 213 (7), 173 (5), 157 (10), 156 (89), 129 (12), 128 (92), 102 (5), 101 (36), 94 (6), 93 (10), 92 (12), 91 (14), 79 (10), 77 (14), 77 (14), 75 (10), 67 (7), 41 (11).

In a similar manner, the following *N*-alkyl-2-quinoline- and 2-quinoxalinecarboxamides were prepared:

N-(1-Adamantyl)-2-quinolinecarboxamide (74)

Prepared from 1,1'-carbonyldiimidazole (160 mg, 0.987 mmol), quinaldic acid (173 mg, 1.00 mmol), and *N,N*-dimethylformamide (2.5 mL) yielding 77 mg (25%) of (74):

rt=10.53 min.; m/z (rel. int.) 306 (M+,91), 305 (26), 277 (9), 263 (9), 221 (11), 172 (9), 171 (73), 145 (15), 144 (60), 143 (15), 136 (11), 135 (100), 128 (36), 117 (19), 116 (27), 107 (20), 105 (8), 101 (10), 93 (42), 91 (30), 89 (14), 81 (13), 79 (55), 77 (37), 67 (18), 65 (11), 55 (12), 53 (10), 41 (18).

N-(2-Adamantyl)-2-quinoxalinecarboxamide (144)

Prepared from 1,1'-carbonyldiimidazole (161 mg, 1.00 mmol), 2-quinoxalinecarboxylic acid (174 mg, 1.00 mmol), 2-adamantanamine (136 mg, 0.90 mmol), and dichloromethane (3.5 mL) yielding 98 mg (35%) of (144):

rt=11.79 min.: m/z (rel. int.) 307 (M+,33), 151 (12), 150 (100), 130 (24), 129 (35), 103 (11), 102 (20), 91 (13), 79 (11), 77 (8), 76 (6), 75 (5), 70 (6), 67 (5), 41 (6).

N-[(1*R*,2*R*,3*R*,5*S*)-3-Pinanemethyl]-2-quinoxalinecarboxamide (151)

Prepared from 1,1'-carbonyldiimidazole (161 mg, 1.00 mmol), 2-quinoxalinecarboxylic acid (174 mg, 1.00 mmol), (-)-3-pinanemethylamine (150 mg, 0.90 mmol), and dichloromethane (3.5 mL) yielding 50 mg (17%) of (151):

rt=11.46 min.; m/z (rel. int.) 323 (M+,7), 187 (76), 186 (10), 174 (25), 166 (15), 158 (44), 157 (20), 144 (6), 131 (10), 130 (78), 129 (100), 107 (8), 103 (21), 102 (44), 95 (15), 93 (10), 91 (9), 81 (11), 79 (13), 77 (12), 76 (14), 75 (11), 69 (8), 67 (17), 55 (20), 53 (10), 51 (7), 43 (10), 41 (30).

EXAMPLE 5: Preparation of *N*-(1-Adamantyl)-2-quinoxalinecarboxamide (91)

2-Quinoxaloyl chloride (0.84 g, 4.4 mmol) was added to a solution of 1-adamantanamine (0.60 g, 4.0 mmol) in pyridine (10 mL). The reaction was then stirred for 30 min. To the stirring reaction mixture was added water (100 mL) which caused the product to precipitate. This precipitate was filtered, washed with water (3 x 25 mL), and dried under high vacuum for 16 h. This provided 1.00 g (82%) of (91):

rt=11.73 min.; m/z (rel. int.) 307 (M+,39), 279 (5), 157 (5), 151 (11), 150 (100), 130 (21), 129 (58), 103 (12), 102 (24), 94 (7), 93 (8), 91 (10), 79 (9), 77 (9), 76 (7), 75 (6), 67 (5), 41 (8), 41 (8).

In a similar manner, the following *N*-substituted 6-quinoline- and 2-quinoxalinecarboxamides were prepared:

_N_-(1-Adamantyl)-6-quinolinecarboxamide (42)

Prepared from 6-quinolinecarbonyl chloride hydrochloride (1.51 g, 10 mmol), 1-adamantanamine (1.73 g, 10 mmol), pyridine (5 mL), and water (200 mL) yielding 330 mg (11%) of (42):

rt=11.04 min.; m/z (rel. int.) 306 (M+,34), 305 (15), 250 (11), 249 (56), 156 (11), 155 (100), 130 (5), 128 (10), 127 (69), 126 (5), 102 (8), 101 (16), 93 (8), 92 (9), 91 (12), 79 (10), 77 (16), 67 (6), 41 (11), 41 (11).

_N_-(_exo_-2-Norbornanyl)-2-quinoxalinecarboxamide (148)

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), *exo*-2-aminonorbornane (133 mg, 0.90 mmol), pyridine (5 mL), and water (50 mL) yielding 35 mg (15%) of (148):

rt=10.22 min.; m/z (rel. int.) 267 (M+,36), 198 (10), 158 (7), 157 (9), 131 (7), 130 (47), 129 (78), 111 (8), 111 (8), 110 (100), 103 (16), 102 (39), 77 (5), 76 (12), 75 (11), 67 (11), 51 (7), 41 (10).

_N_-[(1_R_,2_S_,4_S_)-Bornyl]-2-quinoxalinecarboxamide (150)

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), (*R*)-(+)-bornylamine (138 mg, 0.90 mmol), pyridine (5 mL), and water (50 mL) yielding 140 mg (50%) of (150):

rt=10.79 min.; m/z (rel. int.) 309 (M+,27), 199 (8), 187 (10), 174 (10), 158 (11), 157 (14), 153 (10), 152 (82), 144 (9), 135 (11), 131 (7), 130 (51), 129

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(100), 109 (20), 103 (18), 102 (43), 95 (38), 93 (12), 91 (7), 79 (9), 77 (11), 76 (13), 75 (11), 67 (17), 55 (14), 53 (8), 51 (8), 43 (8), 41 (25).

N-(3-Noradamantyl)-2-quinoxalinecarboxamide (152)

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), 3-noradamantanamine (157 mg, 0.90 mmol), pyridine (5 mL), and water (50 mL) yielding 167 mg (63%) of (152):

rt=11.00 min.; m/z (rel. int.) 293 (M+,50), 265 (12), 250 (18), 232 (6), 222 (20), 157 (12), 144 (6), 137 (7), 136 (64), 131 (6), 130 (35), 130 (35), 129 (100), 103 (19), 102 (35), 94 (15), 91 (6), 80 (6), 79 (11), 77 (11), 76 (12), 75 (9), 67 (6), 53 (6), 51 (6), 41 (13).

N-[(1R,2R,3R,5S)-Isopinocamphenyl]-2-quinoxalinecarboxamide (165)

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), (1R,2R,3R,5S)-(-)-isopinocamphenylamine (138 mg, 0.90 mmol), pyridine (5 mL), and water (50 mL) yielding 230 mg (83%) of (165):

rt=10.88 min.; m/z (rel. int.) 309 (M+,4), 226 (19), 200 (17), 199 (5), 198 (7), 186 (9), 175 (7), 174 (16), 158 (6), 157 (14), 152 (6), 130 (42), 129 (100), 103 (16), 102 (42), 102 (42), 95 (13), 93 (10), 79 (6), 77 (7), 76 (11), 75 (9), 67 (7), 55 (12), 53 (6), 51 (5), 43 (5), 41 (18).

N-[(1S,2S,3S,5R)-Isopinocamphenyl]-2-quinoxalinecarboxamide (166)

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), (1S,2S,3S,5R)-(+)-isopinocamphenylamine (138 mg, 0.90 mmol), pyridine (5 mL), and water (50 mL) yielding 208 mg (75%) of (166):

rt=10.88 min.: m/z (rel. int.) 309 (M+,4), 226 (16), 200 (14), 198 (7), 186 (8), 175 (6), 174 (14), 158 (5), 156 (13), 130 (42), 130 (42), 129 (100), 103 (18), 102 (46), 95 (11), 93 (10), 91 (5), 79 (5), 77 (8), 76 (12), 75 (11), 67 (8), 55 (13), 53 (6), 51 (6), 43 (6), 41 (20).

N-(5-Chlorotricyclo[2.2.1.0(2,6)]hept-3-yl)-2-quinoxalinecarboxamide (167)

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), 5-chlorotricyclo[2.2.1.0(2,6)]hept-3-ylamine (129 mg, 0.90 mmol), pyridine (5 mL), and water (50 mL) yielding 100 mg (37%) of (167):

rt=11.29 min.: m/z (rel. int.) 299 (M+,2), 264 (76), 246 (12), 199 (7), 198 (47), 186 (16), 185 (6), 144 (6), 142 (16), 130 (30), 129 (100), 106 (15), 103 (20), 102 (55), 102 (55), 91 (24), 80 (7), 79 (18), 78 (6), 77 (18), 76 (19), 75 (19), 65 (10), 53 (6), 52 (6), 51 (14), 50 (7).

N-(Tricyclo[4.3.1.1(3,8)]undec-3-yl)-2-quinoxalinecarboxamide (168)

Prepared from 2-quinoxaloyl chloride (135 mg, 0.70 mmol), tricyclo[4.3.1.1(3,8)]undec-3-ylamine hydrochloride (100 mg, 0.60 mmol), pyridine (5 mL), and water (50 mL) yielding 110 mg (57%) of (168):

rt=12.52 min.: m/z (rel. int.) 321 (M+,48), 165 (13), 164 (100), 157 (9), 131 (8), 130 (32), 130 (32), 129 (79), 107 (5), 106 (5), 105 (11), 103 (17), 102 (31), 94 (9), 93 (8), 92 (9), 91 (15), 81 (6), 80 (7), 79 (16), 77 (10), 76 (9), 75 (7), 67 (8), 55 (5), 53 (5), 41 (10).

***N*-[(1*S*,2*R*,5*S*)-*cis*-Myrtanyl]-2-quinoxalinecarboxamide (169)**

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), (-)-*cis*-myrtanylamine (138 mg, 0.90 mmol), pyridine (5 mL), and water (50 mL) yielding 224 mg (81%) of (169):

rt=11.32 min.: m/z (rel. int.) 309 (M+,18), 186 (30), 174 (20), 158 (12), 157 (27), 152 (16), 131 (6), 130 (47), 130 (47), 129 (100), 121 (5), 103 (17), 102 (45), 93 (12), 91 (6), 81 (11), 79 (12), 77 (10), 76 (13), 75 (11), 69 (13), 67 (15), 55 (8), 54 (6), 53 (8), 51 (7), 43 (6), 41 (26).

***N*-[(1*R*,2*R*,4*S*)-Isobornyl]-2-quinoxalinecarboxamide (170)**

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), (*R*)-(-)-isobornylamine (138 mg, 0.90 mmol), pyridine (5 mL), and water (50 mL) yielding 130 mg (81%) of (170):

rt=10.76 min.: m/z (rel. int.) 309 (M+,24), 199 (7), 197 (6), 187 (8), 174 (8), 158 (9), 157 (12), 153 (7), 152 (58), 144 (9), 135 (8), 130 (46), 129 (100), 109 (14), 103 (21), 102 (48), 95 (31), 93 (10), 91 (7), 79 (8), 77 (10), 76 (13), 75 (12), 67 (15), 55 (12), 53 (7), 51 (6), 43 (6), 41 (18).

***N*-[*endo*-(±)-2-Norbornanyl]-2-quinoxalinecarboxamide (171)**

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), *endo*-(±)-2-aminonorbornane (133 mg, 0.90 mmol), pyridine (5 mL), and water (50 mL) yielding 175 mg (73%) of (171):

rt=10.15 min.; m/z (rel. int.) 267 (M+,35), 198 (11), 185 (6), 158 (7), 157 (11), 144 (5), 131 (7), 130 (55), 129 (100), 111 (6), 110 (81), 103 (24), 102 (56), 77 (7), 76 (19), 75 (17), 75 (17), 67 (13), 55 (5), 53 (7), 51 (9), 50 (5), 41 (14).

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N-[(R)-2-Phenyl-1-propyl]-2-quinoxalinecarboxamide (172)

Prepared from 2-quinoxaloyl chloride (0.47 g, 2.4 mmol), (R)-2-phenyl-1-propylamine (0.30 g, 2.2 mmol), pyridine (5 mL), and water (50 mL) yielding 0.49 g (76%) of (172):

rt=10.63 min.: m/z (rel. int.) 291 (M+.14), 186 (9), 158 (5), 157 (32), 130 (25), 129 (100), 118 (22), 105 (24), 104 (5), 103 (21), 102 (48), 91 (9), 79 (11), 78 (6), 77 (18), 76 (13), 75 (13), 75 (13), 51 (9).

N-[(S)-2-Phenyl-1-propyl]-2-quinoxalinecarboxamide (173)

Prepared from 2-quinoxaloyl chloride (0.47 g, 2.4 mmol), (S)-2-phenyl-1-propylamine (0.30 g, 2.2 mmol), pyridine (5 mL), and water (50 mL) yielding 0.48 g (74%) of (173):

rt=10.72 min.: m/z (rel. int.) 291 (M+.13), 186 (68), 158 (5), 157 (37), 130 (21), 129 (100), 118 (29), 105 (21), 103 (16), 102 (37), 91 (7), 79 (10), 77 (15), 76 (11), 75 (10), 51 (9), 51 (9).

N-(2-Indanyl)-2-quinoxalinecarboxamide (221)

Prepared from 2-quinoxaloyl chloride (0.32 g, 1.7 mmol), 2-aminoindan (0.20 g, 1.5 mmol), pyridine (3 mL), and water (30 mL) yielding 0.23 g (53%) of (221):

rt=11.33 min.; m/z (rel. int.) 289 (M+.10), 132 (6), 130 (28), 129 (41), 117 (15), 116 (100), 115 (37), 104 (7), 103 (26), 102 (37), 91 (7), 78 (7), 77 (13), 76 (16), 75 (14), 51 (9), 51 (9), 50 (5).

N-Cyclooctyl-2-quinoxalinecarboxamide (228)

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), cyclooctylamine (123 µL, 114 mg, 0.90 mmol), pyridine (5 mL), and water (100 mL) yielding 100 mg (39%) of (228):

rt=10.86 min.; m/z (rel. int.) 283 (M+,27), 212 (6), 199 (9), 198 (20), 198 (20), 185 (16), 184 (6), 174 (8), 157 (15), 144 (7), 131 (6), 130 (48), 129 (100), 126 (42), 103 (20), 102 (50), 76 (13), 75 (12), 67 (6), 56 (7), 55 (9), 51 (6), 43 (6), 41 (16).

N-Cycloheptyl-2-quinoxalinecarboxamide (229)

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), cycloheptylamine (115 µL, 102 mg, 0.90 mmol), pyridine (5 mL), and water (100 mL) yielding 30 mg (12%) of (229):

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rt=10.30 min.: m/z (rel. int.) 269 (M+,39), 212 (6), 198 (20), 185 (13), 174 (14), 174 (14), 157 (20), 131 (7), 130 (49), 129 (100), 112 (44), 103 (23), 102 (51), 76 (15), 75 (13), 56 (6), 55 (8), 51 (7), 42 (5), 41 (15).

N-[2-Spiro(4.5)decyl]-2-quinoxalinecarboxamide (236)

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), 2-aminospiro(4.5)decane (150 mg, 0.79 mmol), pyridine (5 mL), and water (100 mL) yielding 206 mg (74%) of (236): rt=10.94 min.:

m/z (rel. int.) 282 (M+,25), 199 (7), 186 (6), 157 (10), 130 (32), 129 (96), 125 (40), 110 (10), 109 (100), 108 (15), 103 (14), 102 (55), 98 (6), 97 (27), 96 (25), 84 (9), 82 (18), 76 (15), 75 (16), 70 (55), 69 (7), 68 (13), 56 (7), 55 (8), 53 (6), 51 (9), 43 (8), 42 (36), 41 (14).

EXAMPLE 6: Preparation of 1-Adamantanemethyl 6-quinolyl ether (94)

A mixture of 1-adamantanemethanol (5.00 g, 30.0 mmol) and 6-hydroxyquinoline (13.1 g, 90.2 mmol) in tetrahydrofuran (75 mL) was stirred for 15 min. Then, triphenylphosphine (10.2 g, 39.0 mmol) was added, followed by diethyl azodicarboxylate (6.14 mL, 39.0 mmol). The reaction mixture was refluxed for 18 h. The solvent was then removed by rotary evaporation. The resulting gel was filtered through paper with diethyl ether (3 x 25 mL). The filtrate was rotary evaporated, and the resulting gel was filtered through paper with hexanes (3 x 25 mL). Again the filtrate was rotary evaporated, the resulting gel was filtered through paper with hexanes (3 x 25 mL), and the filtrate was rotary evaporated. This provided 3.8 g (43%) of crude product as a red oil. This oil was chromatographed (2:1 hexanes/ethyl acetate) to provide 1.6 g (18%) of (94):

rt=11.29 min.; m/z (rel. int.) 293 (M+,15), 149 (100), 145 (6), 128 (13), 121 (6), 116 (12), 116 (12), 107 (17), 93 (29), 91 (18), 89 (10), 81 (16), 79 (25), 77 (17), 67 (14), 65 (5), 55 (8), 53 (6), 41 (14).

EXAMPLE 7: Preparation of 1-Adamantyl 3-quinolinecarboxylate (101)

A mixture of 1-adamantanol (152 mg, 1.0 mmol), 3-quinolinecarboxylic acid (173 mg, 1.0 mmol), and dimethylaminopyridine (122 mg, 1.0 mmol) in dichloromethane (2 mL) and *N,N*-dimethylformamide (2 mL) was cooled to 0 °C. 1,3-Dicyclohexylcarbodiimide (227 mg, 1.1 mmol) in dichloromethane (1 mL) was added in one portion. The reaction mixture was stirred at 25 °C for 20 h.

The reaction mixture was then diluted with dichloromethane (40 mL) and washed with 1 M sodium hydroxide (3 x 30 mL). The organic layer was dried (anhydrous magnesium sulfate), filtered through Celite, and rotary evaporated. The resulting material was purified by spinning thin-layer chromatography (3% methanol in chloroform). The purest fraction was rotary evaporated. and the resulting material was recrystallized from ethanol. This provided 42 mg (14%) of (101):

rt=7.78 min.: m/z (rel. int.) 307 (M+,96), 306 (100), 173 (11), 155 (38), 135 (6), 127 (55), 119 (6), 106 (9), 100 (23), 93 (25), 92 (33), 91 (14), 78 (23), 77 (6), 76 (13), 74 (8), 67 (9), 54 (7), 41 (12).

EXAMPLE 8: Preparation of *N*-(α,α-Dimethylphenethyl)-2-quinoxalinecarboxamide (108)

2-Quinoxaloyl chloride (207 mg, 1.07 mmol) in dichloromethane (1 mL) was added to a solution of phentermine (160 mg, 1.07 mmol) in dichloromethane (3 mL) cooled to 0 °C. The reaction was allowed to warm to 25 °C. After 5 min, the reaction mixture was diluted with ethyl acetate (40 mL) and washed with 1 M sodium hydroxide (2 x 40 mL). The organic layer was dried (anhydrous magnesium sulfate), filtered through silica gel, and rotary evaporated. This provided 51 mg (16%) of (108):

rt=9.31 min.: m/z (rel. int.) 305 (M+..0), 214 (96), 186 (30), 157 (16), 130 (22), 129 (100), 103 (10), 102 (31), 92 (4), 91 (47), 76 (5), 75 (5), 65 (10).

N-(2-Chlorobenzyl)-2,4,6-triphenylpyridinium tetrafluoroborate

2-Chlorobenzylamine (2.0 g, 14 mmol) was added dropwise to a suspension of 2,4,6-triphenylpyrylium tetrafluoroborate (5.1 g, 13 mmol) in dichloromethane (40 mL). The reaction mixture was stirred for 16 h. Ethanol (4 mL) and excess diethyl ether were added to precipitate the product. The precipitate was filtered and dried. This provided 6.14 g (92%) of *N*-(2-chlorobenzyl)-2,4,6-triphenylpyridinium tetrafluoroborate.

1-(2-Chlorophenyl)-2-methyl-2-nitropropane

2-Nitropropane (3.19 mL, 35.5 mmol) was added to a mixture of sodium hydride (0.85 g, 35 mmol) in methanol (15 mL) cooled to 0 °C. The reaction mixture was then stirred and allowed to warm to 25 °C for 10 min. The solvent

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was rotary evaporated to provide a white solid. A mixture of this solid and *N*-(2-chlorobenzyl)-2,4,6-triphenylpyridinium tetrafluoroborate (6.14 g, 11.8 mmol) in dimethyl sulfoxide (45 mL) was stirred under nitrogen gas for 16 h. Water was then added to quench the reaction. This mixture was then extracted with diethyl ether (3 x 100 mL). The organic layer was washed with saturated aqueous sodium chloride, dried (anhydrous sodium sulfate), and filtered. The filtrate was stirred in strongly acidic Amberlyst 15 ion-exchange resin (1 g/mmol) for 4 h. The reaction mixture was filtered and rotary evaporated. This provided 2.35 g (93%) of 1-(2-chlorophenyl)-2-methyl-2-nitropropane.

α,α-Dimethyl-2-chlorophenethylamine

A mixture of Raney nickel (50% by weight in water: 2.3 g) and 1-(2-chlorophenyl)-2-methyl-2-nitropropane (2.35 g, 11 mmol) in ethanol (35 mL) was shaken under hydrogen gas (60 psig) for 3.5 h. The reaction mixture was then filtered, and the filtrate was rotary evaporated. This provided 2.3 g (110%) of α,α-dimethyl-2-chlorophenethylamine.

***N*-(α,α-Dimethyl-2-chlorophenethyl)-2-quinoxalinecarboxamide (197)**

In a similar manner to (108), (197) was prepared from 2-quinoxaloyl chloride (158 mg, 0.82 mmol), α,α-dimethyl-2-chlorophenethylamine (151 mg, 0.82 mmol), and dichloromethane (3 mL) yielding 196 mg (70%) of (197): rt=10.04 min.; m/z (rel. int.) 339 (M+,.0), 213 (58), 186 (24), 156 (12), 129 (25), 128 (100), 126 (14), 124 (44), 102 (14), 101 (38), 98 (5), 90 (5), 88 (18), 75 (10), 75 (10), 75 (9), 62 (5), 50 (5), 41 (9).

EXAMPLE 9: Preparation of *N*-(α,α-Dimethyl-4-fluorophenethyl)-2-quinoxalinecarboxamide (129)

To a solution of 1-(4-fluorophenyl)-2-methyl-2-propylamine (105 mg, 0.628 mmol) in pyridine (2 mL) was added 2-quinoxaloyl chloride (133 mg, 0.691 mmol). The reaction was then stirred for 30 min. To the stirring reaction mixture was added water (20 mL) which caused the product to separate as an oil. This mixture was extracted with ethyl acetate (1 x 10 mL), washed with water (2 x 5 mL), dried (anhydrous magnesium sulfate), rotary evaporated, and put under high vacuum for 15 h. This provided 146 mg (71.9%) of (129):

rt=10.45 min.: m/z (rel. int.) 323 (M+,.1), 214 (73), 186 (22), 157 (14), 135 (4), 130 (19), 129 (100), 109 (22), 103 (9), 102 (30), 83 (7), 76 (9), 75 (8), 42 (6).

In a similar manner, the following *N*-substituted 2-quinoxalinecarboxamides were prepared:

_N_-(β-Methylphenethyl)-2-quinoxalinecarboxamide (131)

Prepared from 2-quinoxaloyl chloride (193 mg, 0.84 mmol), β-methylphenethylamine (103 mg, 0.76 mmol), and pyridine (2 mL) yielding 154 mg (69%) of (131):

rt=10.71 min.; m/z (rel. int.) 291 (M+,12), 186 (66), 158 (5), 157 (37), 130 (20), 129 (100), 118 (28), 105 (21), 103 (17), 102 (37), 91 (7), 79 (10), 78 (5), 77 (15), 76 (11), 75 (10), 51 (10), 51 (10).

_N_-(3-Methylcyclohexyl)-2-quinoxalinecarboxamide (161)

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), 3-methylcyclohexylamine (119 mg, 0.90 mmol), and pyridine (5 mL) yielding 190 mg (78%) of (161):

rt=9.99 min.; m/z (rel. int.) 269 (M+,37), 226 (6), 198 (11), 174 (23), 157 (23), 131 (7), 130 (44), 129 (100), 113 (5), 112 (59), 103 (20), 102 (41), 95 (5), 81 (6), 76 (15), 75 (12), 56 (5), 55 (9), 51 (7), 41 (15), 41 (15).

_N_-(2,3-Dimethylcyclohexyl)-2-quinoxalinecarboxamide (163)

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), 2,3-dimethylcyclohexylamine (115 mg, 0.90 mmol), and pyridine (5 mL) yielding 150 mg (59%) of (163):

rt=10.12 min.; m/z (rel. int.) 283 (M+,35), 212 (6), 198 (14), 175 (6), 174 (39), 158 (7), 157 (22), 131 (6), 130 (46), 129 (100), 126 (44), 109 (8), 103 (20), 103 (20), 102 (45), 76 (13), 75 (11), 67 (7), 56 (10), 55 (12), 51 (6), 43 (6), 41 (16).

_N_-[(1*S*,2*S*,3*S*,5*R*)-3-Pinanemethyl]-2-quinoxalinecarboxamide (207)

Prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), (+)-3-pinanemethylamine (150 mg, 0.90 mmol), and pyridine (5 mL) yielding 229 mg (79%) of (207):

rt=12.07 min.; m/z (rel. int.) 323 (M+,12), 187 (100), 186 (12), 174 (33), 166 (24), 159 (8), 158 (66), 157 (26), 150 (9), 144 (7), 131 (11), 130 (80), 129 (85),

107 (10), 103 (14), 102 (31), 95 (22), 93 (11), 91 (8), 83 (7), 81 (11), 79 (11), 77 (8), 76 (8), 69 (8), 67 (13), 55 (17), 43 (9), 41 (25).

EXAMPLE 10: ***N*-(1-Adamantanemethyl)-2-quinoxalinecarboxamide (146)**

2-Quinoxaloyl chloride (429 mg, 2.6 mmol) was added to a solution of 1-adamantanemethylamine (500 mg, 2.6 mmol) in chloroform (5 mL). The reaction mixture was heated until everything had dissolved. The reaction mixture was stirred at 25 °C for 1 h. To the stirring reaction mixture was added water (100 mL) which caused the product to precipitate. The precipitate was filtered, washed with water (2x), and dried under high vacuum. This provided 375 mg (45%) of (146):

rt=12.27 min.; m/z (rel. int.) 321 (M+,101), 186 (7), 174 (6), 164 (34), 158 (6), 157 (8), 136 (11), 135 (100), 131 (7), 130 (46), 129 (75), 107 (23), 105 (6), 103 (20), 102 (53), 93 (44), 92 (6), 91 (23), 81 (13), 79 (47), 77 (24), 76 (16), 75 (13), 67 (16), 65 (6), 55 (9), 53 (8), 51 (8), 41 (13).

EXAMPLE 11: **Preparation of *N*-(4-Methylcyclohexyl)-2-quinoxalinecarboxamide (162)**

To a solution of 4-methylcyclohexylamine (119 mg, 0.90 mmol) in pyridine (2 mL) was added 2-quinoxaloyl chloride (193 mg, 1.0 mmol). The reaction was then stirred for 1 h. To the stirring reaction mixture was added water (20 mL) which caused the product to precipitate as an oil. This mixture was extracted with 30% dichloromethane in diethyl ether (2 x 25 mL), washed with water (2 x 25 mL), dried (anhydrous sodium sulfate), and rotary evaporated. This provided 123 mg (51%) of (162):

rt=10.00 min.; m/z (rel. int.) 269 (M+,53), 212 (15), 212 (15), 198 (7), 174 (25), 158 (6), 157 (36), 131 (7), 130 (44), 129 (100), 113 (6), 112 (66), 103 (18), 102 (36), 95 (9), 81 (6), 76 (12), 75 (9), 56 (5), 55 (10), 51 (6), 41 (12).

EXAMPLE 12: **Preparation of *N*-[(1*S*,2*S*,5*S*)-*trans*-Myrtanyl]-2-quinoxalinecarboxamide (225)**

(1*S*,2*S*,5*S*)-*trans*-Myrtanyl trifluoroacetate

Trifluoroacetic anhydride (5.50 mL, 39.0 mmol) was added to (-)-*trans*-myrtanol (5.10 mL, 32.5 mmol) in dry tetrahydrofuran (100 mL). This reaction

mixture was stirred for 1 h. The reaction mixture was rotary evaporated. This provided 7.60 g (94%) of (1*S*,2*S*,5*S*)-*trans*-myrtanyl trifluoroacetate.

(1*R*,2*R*,5*R*)-*trans*-Myrtanyl trifluoroacetate

In a similar manner, (1*R*,2*R*,5*R*)-*trans*-myrtanyl trifluoroacetate was prepared from trifluoroacetic anhydride (5.40 mL, 38.0 mmol, 1.2 equiv) (+)-*trans*-myrtanol (5.00 mL, 4.90 g, 31.7 mmol), and tetrahydrofuran (100 mL) yielding 7.60 g (94%) of (1*R*,2*R*,5*R*)-*trans*-myrtanyl trifluoroacetate.

(1*S*,2*S*,5*S*)-*trans*-Myrtanylazide

A mixture of (1*S*,2*S*,5*S*)-*trans*-myrtanyl trifluoroacetate (1.0 g, 4.0 mmol), sodium azide (0.39 g, 6.0 mmol), and *N*,*N*-dimethylformamide (50 mL) was stirred at 80 °C for 24 h. After cooling to 25 °C, water (100 mL) was added, and this mixture was extracted with diethyl ether (2 x 50 mL). The organic layer was then dried (anhydrous sodium sulfate) and rotary evaporated. This provided 1.12 g (100%) of (1*S*,2*S*,5*S*)-*trans*-myrtanylazide as a colorless oil.

(1*R*,2*R*,5*R*)-*trans*-Myrtanylazide

In a similar manner, (1*R*,2*R*,5*R*)-*trans*-myrtanylazide was prepared from (1*R*,2*R*,5*R*)-*trans*-myrtanyl trifluoroacetate (7.60 g, 30.4 mmol), sodium azide (3.00 g, 45.6 mmol), and *N*,*N*-dimethylformamide (100 mL) yielding 4.10 g (48.2%) of (1*R*,2*R*,5*R*)-*trans*-myrtanylazide.

(1*S*,2*S*,5*S*)-*trans*-Myrtanylamine

A mixture of (1*S*,2*S*,5*S*)-*trans*-myrtanylazide (1.12 g, 7.32 mmol) and platinum(IV) oxide hydrate (0.34 g) in ethanol (50 mL) was shaken under hydrogen gas (50 psig) for 2 h. The reaction mixture was then filtered through paper, and the filtrate was rotary evaporated. The resulting material was taken up in 0.12 M hydrochloric acid (100 mL), and the aqueous solution was washed with diethyl ether (2 x 50 mL). The aqueous layer was made basic with 0.1 M sodium hydroxide (50 mL) and extracted with dichloromethane (2 x 50 mL). The organic layer was then dried (anhydrous sodium sulfate) and rotary

evaporated. This provided 78 mg (7%) of (1*S*,2*S*,5*S*)-*trans*-myrtanylamine as a light yellow oil.

(1*R*,2*R*,5*R*)-*trans*-Myrtanylamine

In a similar manner, (1*R*,2*R*,5*R*)-*trans*-myrtanylamine was prepared from (1*R*,2*R*,5*R*)-*trans*-myrtanylazide (4.10 g, 26.8 mmol), platinum(IV) oxide hydrate (0.41 g), and ethanol (75 mL) yielding 2.00 g (48.8%) of (1*R*,2*R*,5*R*)-*trans*-myrtanylamine.

***N*-[(1*S*,2*S*,5*S*)-*trans*-Myrtanyl]-2-quinoxalinecarboxamide (225)**

In a similar manner to (162), (225) was prepared from 2-quinoxaloyl chloride (49 mg, 0.25 mmol), (1*S*,2*S*,5*S*)-*trans*-myrtanylamine (35 mg, 0.23 mmol), and pyridine (5 mL) yielding 8 mg (10%) of (225):

rt=11.23 min.; m/z (rel. int.) 309 (M+,25), 187 (15), 186 (39), 174 (12), 158 (14), 157 (29), 152 (20), 131 (6), 130 (47), 130 (47), 129 (100), 103 (15), 102 (41), 93 (9), 91 (6), 81 (12), 79 (12), 77 (9), 76 (11), 75 (10), 69 (14), 67 (17), 55 (8), 54 (5), 53 (7), 51 (7), 43 (6), 41 (25).

***N*-[(1*R*,2*R*,5*R*)-*trans*-Myrtanyl]-2-quinoxalinecarboxamide (226)**

In a similar manner, (226) was prepared from 2-quinoxaloyl chloride (193 mg, 1.0 mmol), (1*R*,2*R*,5*R*)-*trans*-myrtanylamine (138 mg, 0.90 mmol), and pyridine (5 mL) yielding 27 mg (10%) of (226):

rt=11.19 min.; m/z (rel. int.) 309 (M+,21), 186 (47), 186 (18), 174 (17), 158 (16), 157 (34), 152 (30), 131 (6), 130 (47), 130 (47), 129 (100), 121 (6), 103 (15), 102 (40), 93 (11), 91 (6), 81 (12), 79 (11), 77 (8), 76 (10), 75 (9), 69 (14), 67 (17), 55 (7), 53 (6), 51 (5), 43 (5), 41 (18).

EXAMPLE 13: Preparation of *N*-[*N'*-(*R*)-α-Methylbenzyl-2-acetamido]-3-aminoquinoline dihydrochloride (156)

***N*-(*R*)-α-Methylbenzyl-2-chloroacetamide**

(*R*)-α-Methylbenzylamine (2.4 g, 20 mmol) in dichloromethane (50 mL) was added to chloroacetyl chloride (2.25 g, 20 mmol) in dichloromethane (70 mL) and pyridine (10 mL). The reaction solution was stirred, then diluted with diethyl ether (500 mL), washed with water (3 x 30 mL), dried (anhydrous magnesium sulfate), and rotary evaporated. This provided 3.60 g of *N*-(*R*)-α-methylbenzyl-2-chloroacetamide.

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N-(R)-α-Methylbenzyl-2-iodoacetamide

A solution of sodium iodide (10.37 g, 69 mmol) in dry acetone was slowly added to a solution of N-(R)-α-methylbenzyl-2-chloroacetamide (3.39 g, 17 mmol) in dry acetone, and the reaction mixture was refluxed for 16 h. The reaction mixture was then filtered, and the filtrate was rotary evaporated. Diethyl ether was added, and the mixture was stirred for 20 min. The mixture was then filtered, and the filtrate was rotary evaporated and then put under high vacuum to provide N-(R)- -methylbenzyl-2-iodoacetamide.

N-[N'-(R)-α-Methylbenzyl-2-acetamido]-3-aminoquinoline dihydrochloride (156)

A mixture of 3-aminoquinoline (0.15 g, 1.0 mmol) and potassium fluoride on Celite (50%) (0.30 g, 2.5 mmol) in acetonitrile (20 mL) was stirred for 1 h. N-(R)-α-Methylbenzyl-2-iodoacetamide (0.31 g, 1.0 mmol) in acetonitrile was added, and the reaction mixture was refluxed for 64 h. The mixture was filtered, and the filtrate was rotary evaporated. The resulting material was taken up in diethyl ether and washed with 1 M sodium hydroxide (3 x 30 mL). The combined aqueous layers were saturated with sodium chloride and were then extracted with chloroform (4x). The combined organic layer were dried (anhydrous magnesium sulfate) and rotary evaporated. The resulting material was dissolved in chloroform (10 mL), 1 M hydrogen chloride in diethyl ether (5 mL) was added, and the solution was rotary evaporated. The resulting material was dissolved in chloroform (5 mL) and filtered through a 0.45 μm filter disc, and the filtrate was evaporated. This provided 13 mg (3%) of (156): rt=10.43 min.; m/z (rel. int.) 328 (M+,11), 182 (12), 181 (86), 180 (37), 167 (22), 166 (25), 165 (17), 162 (53), 161 (95), 160 (37), 148 (32), 145 (18), 135 (21), 132 (16), 122 (9), 120 (22), 119 (20), 107 (19), 106 (13), 105 (100), 104 (22), 103 (19), 90 (12), 79 (25), 78 (11), 77 (38), 51 (10), 44 (10), 41 (11).

EXAMPLE 14: Preparation of 1-(1-Adamantyl)-2-(benzothiazol-2-ylsulfanyl)ethanone (273)

Sodium hydride (36.5 mg, 1.52 mmol, 60% in mineral oil) was washed with pentane (4X), dried under N_2, suspended in dimethylformamide (DMF, 10

mL) and cooled to 0 °C. With stirring, a solution of 2-mercaptobenzothiazole (253.3 mg, 1.52 mmol) in DMF (5 mL) was added dropwise. The reaction was stirred 20 minutes at 0°C and treated with a solution of 1-adamantanebromomethyl ketone (389.8 mg, 1.52 mmol) in DMF (8 mL). The reaction was stirred 30 minutes at ambient temperature and diluted with diethyl ether (100 mL). The resulting solution was washed with water (5 x 30 mL) and the remaining organic solution dried over anhydrous $MgSO_4$, filtered, and concentrated to a solid. Recrystallization from hot ethanol afforded 287 mg (55%) of the desired product: GC/EI-MS gave *m/z* (rel. int.) 343 (M^+, 10), 315 (2), 180 (2), 148 (10), 135 (100), 107 (9), 93 (17), and 79 (20).

EXAMPLE 15: Assay of mGluR Group I antagonist activity

HEK-293 cells expressing a recombinant receptor as described in WO 97/05252 were loaded with 2 μM Fura-2 acetoxymethylester by incubation for 30-40 minutes at 37 °C in SPF-PCB (126 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 20 mM Na-HEPES, 1.0 mM $CaCl_2$, 1 mg/mL glucose, and 0.5% BSA, pH 7.4).

The cells were washed 1-2 times in SPF-PCB, resuspended to a density of 4-5 million cells/mL and kept at 37 °C in a plastic beaker. For recording fluorescent signals, the cells were diluted five-fold into a quartz cuvette with BSA-free 37 °C SPF-PCB to achieve a final BSA concentration of 0.1% (1.2 mL of 37 °C BSA-free SPF-PCB + 0.3 mL cell suspension). Measurements of fluorescence were performed at 37 °C with constant stirring using a custom-built spectrofluorimeter (Biomedical Instrumentation Group, University of Pennsylvania). Excitation and emission wavelengths were 340 and 510 nm, respectively. To calibrate fluorescence signals, digitonin (Sigma Chemical Co., St. Louis, MO; catalog # D-5628; 50 μg/mL, final) was added to obtain maximal fluorescence (F_{max}), and the apparent minimal fluorescence (F_{min}) was determined by adding TRIS-Base/EGTA (10 mM, pH 8.3, final). Concentrations of intracellular Ca^{2+} were calculated using a dissociation constant (Kd) of 224 nM and applying the equation:

$$[Ca^{2+}]_i = (F - F_{min} / F_{max}) \times Kd;$$

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where F is fluorescence measured at any particular time of interest and F falls between F_{max} and F_{min}.

Control responses to the addition of 5 mM Ca^{2+} (final extracellular calcium concentration. 6 mM) were determined in separate cuvettes. Control responses to changes in extracellular calcium were determined throughout the length of the experiment. Compounds were tested at a single concentration per cuvette of cells, and all compounds were prepared in DMSO. Appropriate dilutions were made such that compounds were added in no greater volume than 10 μl per a total volume of 1500 μl (final DMSO not greater than 0.67%) to achieve any particular testing concentration.

Once a stable intracellular calcium baseline was achieved. the compound was added to the cuvette. The response or lack of response to the compound addition was allowed to stabilize for 1-3 minutes and then 5 mM calcium was added to determine the effect of the compound on the subsequent calcium response. Once the peak for the subsequent calcium response was obtained. digitionin and EGTA were added in a sequential manner to determine F_{max} and F_{min}, respectively. Data were expressed as changes in intracellular calcium concentrations in nM. These changes in the calcium response post compound addition were compared to the control (no compound) calcium response. Responses to calcium in the presence of test compounds were normalized as a percent change from that of controls. Data were entered into a Levenberg-Marquardt analysis for non-linear least squares and an IC_{50} and 95% confidence intervals thereof were determined for each compound.

The invention thus has been disclosed broadly and illustrated in reference to representative embodiments described above. Those skilled in the art will recognize that various modifications can be made to the present invention without departing from the spirit and scope thereof.

What is claimed is:

1. A compound represented by the formula I,

$$R-[\text{Linker}]-Ar$$

wherein R is an optionally substituted straight or branched chain alkyl, aralkyl, cycloalkyl, or alkylcycloalkyl group containing 5-12 carbon atoms,

wherein Ar is an optionally substituted aromatic, heteroaromatic, aralkyl, or heteroaralkyl moiety containing up to 10 carbon atoms and up to 4 heteroatoms, and

wherein [linker] is $-(CH_2)_n-$, where n is 2-6, and wherein up to 4 CH_2 groups may independently be substituted with groups selected from the group consisting of C_1-C_3 alkyl, CHOH, CO, O, S, SO, SO_2, N, NH, and NO, provided that two heteroatoms may not be adjacent except when those atoms are both N or are both NH, and wherein any two adjacent CH_2 groups may be replaced by a substituted or unsubstituted alkene or alkyne group,

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein Ar comprises a ring system selected from the group consisting of benzene, thiazole, furyl, pyranyl, 2H-pyrrolyl, thienyl, pyrollyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl benzothiazole, benzimidazole, 3H-indolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalizinyl, naphthyridinyl, quinazolinyl, cinnolinyl, isothiazolyl, quinoxalinyl indolizinyl, isoindolyl, benzothienyl, benzofuranyl, isobenzofuranyl, and chromenyl rings,

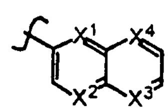
wherein Ar optionally may independently be substituted with up to two C_1-C_3 alkyl groups, or up to two halogen atoms, where halogen is selected from F, Cl, Br, and I.

3. The compound according to claim 1, wherein R contains 7-11 carbon atoms, wherein some or all of the hydrogen atoms on two carbon atoms optionally may be replaced with substituents independently selected from the group consisting of F, Cl, OH, OMe, and =O.

4. The compound according to claim 1, wherein [linker] comprises an amide, ester, or thioester group.

5. The compound according to claim 3, wherein R comprises a moiety selected from the group consisting of adamantyl, 2-adamantyl, (1S,2S,3S,5R)-isopinocamphenyl, tricyclo[4.3.1.1(3,8)]undec-3-yl, (1S,2R,5S)-*cis*-myrtanyl, (1R,2R,4S)-isobornyl (1R,2R,3R,5S)-isopinocamphenyl, (1S,2S,5S)-*trans*-myrtanyl, (1R,2R,5R)-*trans*-myrtanyl, (1R,2S,4S)-bornyl, 1-adamantanemethyl, 3-noradamantyl, (1S,2S,3S,5R)-3-pinanemethyl, cyclooctyl, α,α-dimethylphenethyl, (S)-2-phenyl-1-propyl, cycloheptyl, 4-methyl-2-hexyl groups, 2,2,3,3,4,4,4-heptafluorobutyl, 4-ketoadamantyl, 3-phenyl-2-methylpropyl, 3,5-dimethyladamantyl, *trans*-2-phenylcyclopropyl, 2-methylcyclohexyl, 3,3,5-trimethylcyclohexyl, 2-(*o*-methoxyphenyl)ethyl, 2-(1,2,3,4-tetrahydronaphthyl), 4-phenylbutyl, 2-methyl-2-phenylbutyl, 2-(m-fluorophenyl)ethyl, 2-(p-fluorophenyl)ethyl, 2-(3-hydroxy-3-phenyl)propyl, (S)-2-hydroxy-2-phenylethyl, (R)-2-hydroxy-2-phenylethyl, 2-(3-*m*-chlorophenyl-2-methyl)propyl, 2-(3-*p*-chlorophenyl-2-methyl)propyl, 4-*tert*-butyl-cyclohexyl, (S)-1-(cyclohexyl)ethyl, 2-(3-(3,4-dimethylphenyl)-2-methyl)propyl, 3,3-dimethylbutyl, 2-(5-methyl)hexyl, 1-myrtanyl, 2-bornyl, 3-pinanemethyl, 2,2,3,3,4,4,5,5-octafluoropentyl, *p*-fluoro-α,α-dimethylphenethyl, 2-naphthyl, 2-bornanyl, cyclohexylmethyl, 3-methylcyclohexyl, 4-methylcyclohexyl, 3,4-dimethylcyclohexyl, 5-chloro-tricyclo[2.2.1]heptyl, *o*-α,α-dimethylphenethyl, 2-indanyl, 2-spiro[4.5]decyl, 2-phenylethyl, 1-adamantylethyl, 1-(1-bicyclo[2.2.1]hept-2-yl)ethyl, 2-(2-methyl-2-phenylpropyl), 2-(*o*-fluorophenyl)ethyl, 1-(cyclohexyl)ethyl, and cyclohexyl.

6. The compound according to claim 1, wherein Ar comprises a group having the formula



wherein X^1, X^2, X^3, and X^4 independently can be N or CH, provided that not more than two of X^1, X^2, X^3, and X^4 can be N.

7. The compound according to claim 6, wherein X^1 is N.

8. The compound according to claim 7, wherein X^2 is N.

9. The compound according to claim 6, wherein X^3 is N.

10. The compound according to claim 6, wherein X^1 is CH and X^2 is N.

11. The compound according to claim 1, wherein Ar is an optionally substituted 2-, 3-, or 4-pyridyl moiety.

12. The compound according to claim 1, wherein Ar is a 6-benzothiazolyl moiety.

13. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable diluent or excipient.

14. A method of making a compound according to claim 4, comprising reacting a compound containing an activated carboxylic acid group with a compound containing an amine, hydroxyl, or thiol group.

15. A method of inhibiting activation of an mGluR Group I receptor, comprising treating a cell containing said receptor with an effective amount of a compound according to claim 1.

16. A method of inhibiting neuronal damage caused by excitatory activation of an mGluR Group I receptor, comprising treating neurons with an effective amount of a compound according to claim 1.

17. A method of treating a disease associated with glutamate-induced neuronal damage, comprising administering to a patient suffering from said disease an effective amount of a composition according to claim 13.

18. The compound according to claim 1, wherein said compound is selected from the group consisting of *N*-[6-(2-Methylquinolyl)]-1-adamantanecarboxamide, *N*-(6-Quinolyl)-1-adamantanecarboxamide, *N*-(2-Quinolyl)-1-adamantanecarboxamide, *N*-(3-Quinolyl)-1-adamantane-carboxamide, 6-Quinolyl-1-adamantanecarboxylate, 1-Adamantyl-6-quinolinecarboxylate, 2,2,3,3,4,4,5,5-Octafluoro-1-pentyl-6-quinolinecarboxylate, 1-Adamantanemethyl-6-quinolinecarboxylate, 1-Adamantyl-2-quinoxalinecarboxylate, *N*-(1-Adamantyl)-3-quinoline-carboxamide, *N*-(1-Adamantyl)-2-quinolinecarboxamide, *N*-(2-Adamantyl)-2-quinoxalinecarboxamide, *N*-[(1R,2R,3R,5S)-3-Pinanemethyl]-2-quinoxaline-carboxamide, *N*-(1-Adamantyl)-2-quinoxalinecarboxamide, *N*-(1-Adamantyl)-6-quinolinecarboxamide, *N*-(*exo*-2-Norbornanyl)-2-quinoxalinecarboxamide, *N*-[(1R,2S,4S)-Bornyl]-2-quinoxalinecarboxamide, *N*-(3-Noradamantyl)-2-quinoxalinecarboxamide, *N*-[(1R,2R,3R,5S)Iso-pinocamphenyl]-2-quinoxalinecarboxamide, *N*-[(1S,2S,3S,5R)-Isopinocamphenyl]-2-quinoxaline-carboxamide, *N*-(5-Chloro-[2.2.1.0]tricyclo-2,6-hepta-3-yl)-2-quinoxalinecarboxamide, *N*-([4.3.1.1)Tricyclo-3,8-undeca-3-yl)-2-quinoxalinecarboxamide, *N*-[(1S,2R,5S)-cis-Myrtanyl]-2-quinoxalinecarboxamide, *N*-[(1R,2R,4S)Isobornyl]-2-quinoxalinecarboxamide, *N*-[endo-(±)-2-Norbornanyl]-2-quinoxalinecarboxamide, *N*-[(R)-2-Phenyl-1 propyl]-2-quinoxalinecarboxamide, *N*-[(S)-2-Phenyl-1-propyl]-2-quinoxalinecarboxamide, *N*-(2-Indanyl)-2-quinoxalinecarboxamide, 1-Adamantanemethyl 6-quinolyl ether, 1-Adamantyl-3-quinolinecarboxylate, *N*-(α,α-Dimethylphenethyl)-2-quinoxalinecarboxamide, *N*-(α,α-Dimethyl-2-chlorophenethyl)-2-quinoxalinecarboxamide, *N*-(α,α-Dimethyl-4-fluorophenethyl)-2-quinoxalinecarboxamide, *N*-(β-Methylphenethyl)-2-quinoxalinecarboxamide, *N*-(3-Methylcyclohexyl)-2-quinoxalinecarboxamide, *N*-(2,3-Dimethylcyclohexyl)-2-quinoxalinecarboxamide, *N*-[(1S,2S,3S,SR)-3-Pinanemethyl]-2-quinoxaline-carboxamide, *N*-(1-Adamantanemethyl)-2-quinoxaline-carboxamide, *N*-(4-Methylcyclohexyl)-2-quinoxaline-carboxamide, *N*-[(1S,2S,5S)-*trans*-Myrtanyl]-2-quinoxaline-carboxamide, and *N*-[(1R,2R,5R)-*trans*-Myrtanyl]-2-quinoxalinecarboxamide, and pharmaceutically acceptable salts thereof.

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19. The compound according to claim 1, wherein said compound is selected from the group consisting of *N*-(1-Adamantyl)-3-quinolinecarboxamide. *N*-(1-Adamantyl)-2-quinolinecarboxamide, *N*-(2-Adamantyl)-2-quinoxaline-carboxamide, *N*-[(1R,2R,3R,5S)-3-Pinanemethyl]-2-quinoxaline-carboxamide, *N*-(1-Adamantyl)-2-quinoxaline-carboxamide, *N*-(1-Adamantyl)-6-quinolinecarboxamide, *N*-(*exo*-2-Norbornanyl)-2-quinoxaline-carboxamide, *N*-[(1R,2S,4S)-Bornyl]-2-quinoxaline-carboxamide, *N*-(3-Noradamantyl)-2-quinoxaline-carboxamide, *N*-[(1R,2R,3R,5S)-Isopinocamphenyl]-2-quinoxaline-carboxamide, *N*-[(1S,2S,3S,5R)-Isopinocamphenyl]-2-quinoxaline-carboxamide. *N*-(5-Chloro-[2.2.1.0]tricyclo-2,6-hepta-3-yl)-2-quinoxaline-carboxamide. *N*-([4.3.1.1]Tricyclo-3,8-undeca-3-yl)-2-quinoxaline-carboxamide. *N*-[(1S,2R,5S)-*cis*-Myrtanyl]-2-quinoxaline-carboxamide, *N*-[(1R,2R,4S)Isobornyl)-2-quinoxaline-carboxamide. *N*-[*endo*-(±)-2-Norbornanyl]-2-quinoxaline-carboxamide, *N*-[(1S,2S,3S,5R)-3-Pinanemethyl]-2-quinoxalinecarboxamide, *N*-(1-Adamantanemethyl)-2-quinoxalinecarboxamide, *N*-[(1S,2S,5S)-*trans*-Myrtanyl]-2-quinoxalinecarboxamide, and *N*-[(1R,2R,5R)-*trans*-Myrtanyl]-2-quinoxalinecarboxamide, and pharmaceutically acceptable salts thereof.

20. The compound according to claim 1, wherein said compound is selected from the group consisting of *N*-[6-(2-Methylquinolyl)]-1-adamantanecarboxamide, *N*-(6-Quinolyl)-1-adamantanecarboxamide. *N*-(2-Quinolyl)-1-adamantanecarboxamide, and *N*-(3-Quinolyl)-1-adamantanecarboxamide, and pharmaceutically acceptable salts thereof

21. The compound according to claim 1, wherein said compound is selected from the group consisting of *N*-(3-Methylcyclohexyl)-2-quinoxalinecarboxamide, *N*-(2,3-Dimethylcyclohexyl)-2-quinoxalinecarboxamide. *N*-[(1S,2S,3S,5R)-3-Pinanemethyl]-2-quinoxalinecarboxamide, *N*-(1-Adamantanemethyl)-2-quinoxalinecarboxamide, and *N*-(4-Methylcyclohexyl)-2-quinoxalinecarboxamide. and pharmaceutically acceptable salts thereof.

22. The compound according to claim 1, wherein said compound is selected from the group consisting of *N*-[(R)-2-Phenyl-1-propyl-2-

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quinoxalinecarboxamide. *N*-[(S)-2-Phenyl-1-propyl]-2-quinoxalinecarboxamide. *N*-(2-Indanyl)-2-quinoxalinecarboxanride. *N*-(α-α-Dimethylphenethyl)-2-quinoxalinecarboxamide. *N*-(α,α-Dimethyl-2-chlorophenethyl)-2-quinoxalinecarboxamide. *N*-(α,α-Dimethyl-4-fluorophenethyl)-2-quinoxaline-carboxamide, and *N*-(β-Methylphenethyl)-2-quinoxaline-carboxamide, and pharmaceutically acceptable salts thereof.

23. The compound according to claim 1, wherein said compound is 1-Adamantanemethyl 6-quinolyl ether, or a pharmaceutically acceptable salt thereof.

24. The compound according to claim 1, wherein said compound is selected from the group consisting of 6-Quinolyl-1-adamantanecarboxylate. 1-Adamantyl-6-quinolinecarboxylate, 2,2,3,3,4,4,5,5-Octafluoro-1-pentyl 6-quinolinecarboxylate, 1-Adamantanemethyl 6-quinolinecarboxylate. 1-Adamantyl-2-quinoxalinecarboxylate. and 1-Adamantyl-3-quinolinecarboxylate. and pharmaceutically acceptable salts thereof.

25. The compound according to claim 1, wherein said compound is selected from the group consisting of 3-(1-Adamantanemethoxy)-2-chloroquinoxaline. 2-(1-Adamantanemethoxy)-3-methylquinoxaline, 3-(1-Adamantanemethoxy)-2-fluoroquinoxaline. 2-(1-Adamantanemethoxy)-3-trifluoromethylquinoxaline, *N*-[2-(4-Phenylthiazolyl)]-1-adamantanecarboxamide. *N*-[2-(5-Methyl-4-phenylthiazolyl)]-1-adamantanecarboxamide. 1-(1-Adamantyl)-2-(benzothiazol-2-ylsulfanyl)ethanone, *N*-(1-Adamantyl)-2-chloroquinoxaline-3-carboxamide. *N*-(1-Adamantyl)-3-methylquinoxaline-2-carboxamide. and *N*-(1-Adamantyl)-1-oxyquinoxaline-3-carboxamide, and pharmaceutically acceptable salts thereof.

26. The compound according to claim1, wherein said compound is selected from the group consisting of 4-Chlorophenyl 3-coumarincarboxylate. 2-(1-Adamantanemethylsulfanyl)quinoxaline, 3-(1-Adamantanemethoxy)-2-chloropyrazine. 1-(1-Adamantyl)-2-(4, 6-dimethylpyrimidin-2-

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ylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(2-anisylsulfanyl)ethanone, 3-(1-Adamantanemethoxy)-1*H*-quinoxalin-2-one, 1-(1-Adamantyl)-2-(3-anisylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(4-anisylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(4-chlorophenylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(2-naphthylsulfanyl)ethanone, *N*-(2-[6-(1-Piperidinyl)pyrazinyl])-1-adamantanecarboxamide, *N*-(2-[6-(1-Piperidinyl)pyrazinyl])adamantan-1-ylmethylcarboxamide, 1-(1-Adamantyl)-2-(1-naphthylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(8-quinolylsulfanyl)ethanone hydrochloride, 1-(1-Adamantyl)-2-(4-trifluoromethoxyphenoxy)ethanone, 2-(1-Adamantanemethoxy)quinoxaline, *N*-(*trans*-4-Methylcyclohexyl)-2-quinoxalinecarboxamide, *N*-(*cis*-4-Methylcyclohexyl)-2-quinoxalinecarboxamide, *N*-(*trans*-4-Methylcyclohexyl)-2-quinolinecarboxamide, *N*-(*trans*-4-Methylcyclohexyl)-3-quinolinecarboxamide, and *N*-(*trans*-4-Methylcyclohexyl)-6-quinolinecarboxamide, and pharmaceutically acceptable salts thereof.

27. The compound according to claim1, wherein said compound is selected from the group consisting of 2-(1-Adamantanemethylsulfinyl)-benzothiazole, *N*-(4-Phenylbutyl)-2-quinoxalinecarboxamide, 1-(1-Adamantyl)-2-(4, 6-dimethylpyrimidin-2-ylsulfanyl)ethanol, 1-(1-Adamantyl)-2-(3-chloroquinoxal-2-yl)ethanone, 2-(1-Adamantanemethylsulfanyl)-3-methylquinoxaline, *N*-(1-Adamantyl)-2-anisamide, *N*-(1-Adamantanemethyl)-2-anisamide, 1-(1-Adamantyl)-2-(4-chlorophenylsulfanyl)ethanone, 2-(1-Adamantanemethylsulfonyl)-3-methylquinoxaline, 1-(1-Adamantyl)-2-(4-fluorophenylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(3-fluorophenylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(2-methoxyphenoxy)ethanone, 1-(4-Anisylsulfanyl)butan-2-one, 1-(1-Adamantyl)-2-(4-anisidinyl)ethanone hydrochloride, 3, 3-Dimethyl-1-(4-anisylsulfanyl)butan-2-one, 1-(4-Biphenyl)-2-(4-anisylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(2-trifluoromethoxyphenylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(3-methylquinoxal-2-ylsulfanyl)ethanone, 1-(1-Adamantyl)-2-(2-anisidinyl)ethanone hydrochloride, 1-(1-Adamantyl)-2-(4-trifluoromethoxyphenylamino)ethanone hydrochloride, 1-(1-Adamantyl)-2-(*N*-methyl-4-anisidinyl)ethanone hydrochloride, *N*-(1-Adamantyl)-7-trifluoromethylquinoline-3-carboxamide, *N*-(1-Adamantyl)-2-(1-piperizinyl)quinoxaline-3-carboxamide, *N*-(1-Adamantyl)-2-(2-

aminoethylamino)quinoxaline-3-carboxamide, Methyl *N*-(3-quinolyl)-3-carboxyadamantane-1-carboxamide, 1-(1-Adamantyl)-2-[(*R*)-1-(1-naphthyl)ethan-1-ylamino]ethanone, *N*-(1-Adamantyl)-2-methoxyquinoxaline-3-carboxamide, Ethyl *N*-(1-adamantyl)-2-(3-propanoylamino)quinoxaline-3-carboxamide, *N*-(4-Chlorophenyl)-2, 3-dimethylquinoxaline-6-carboxamide, *N*-(1-Adamantyl)-6, 7-dimethylquinoxaline-2-carboxamide, *N*-((*S*)-1-Tetralinyl)-2-quinoxalinecarboxamide, *N*-(4-Chlorophenethyl)-2-quinoxalinecarboxamide, *N*-(6-Quinolyl)-2-quinoxalinecarboxamide, *N*-(1-Tetralinmethyl)-2-quinoxalinecarboxamide, *N*-(1-Indanmethyl)-2-quinoxalinecarboxamide, *N*-(4, 4-Dimethylcyclohexyl)-2-quinoxalinecarboxamide, and pharmaceutically acceptable salts thereof.

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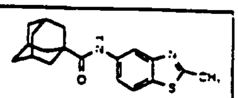
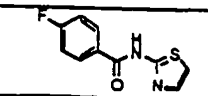
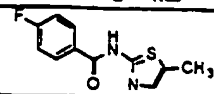
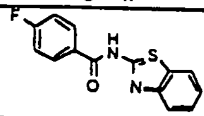
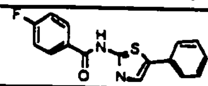
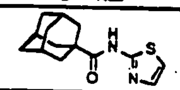
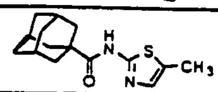
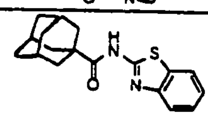
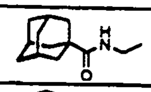
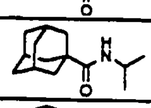
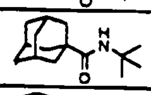
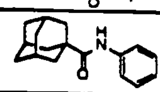
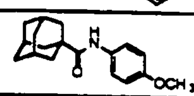
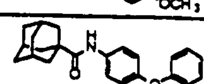
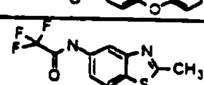
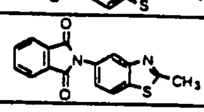
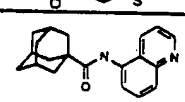
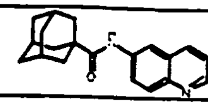
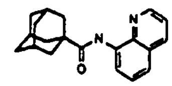
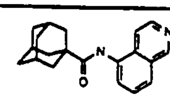
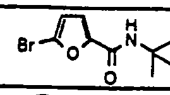
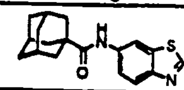
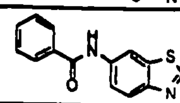
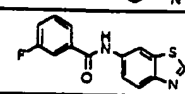
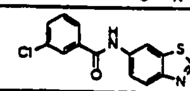
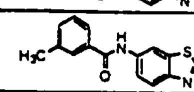
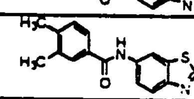
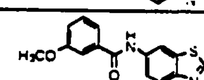
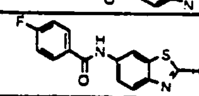
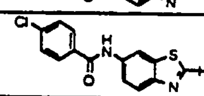
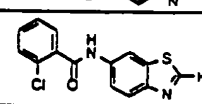
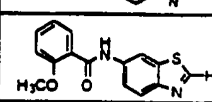
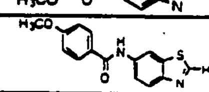
Figure 1

1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	

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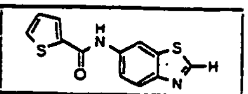
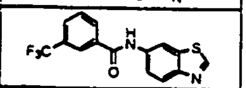
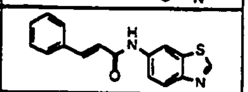
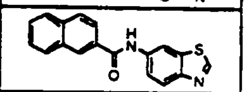
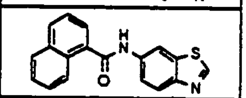
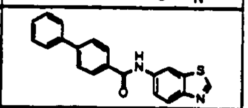
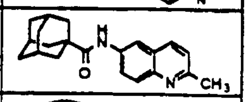
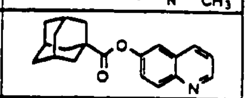
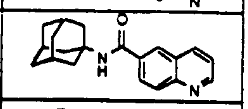
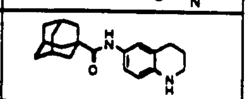
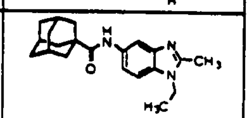
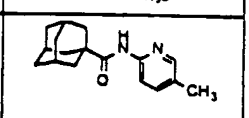
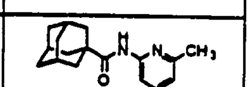
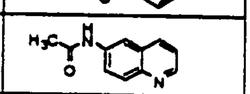
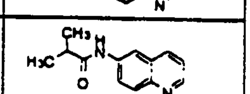
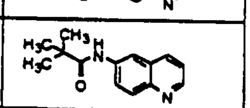
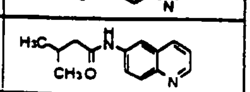
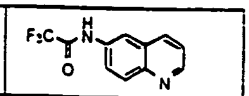
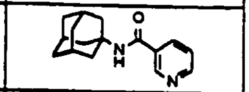
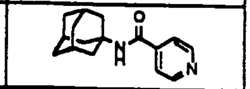
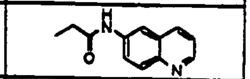
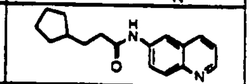
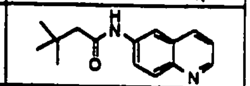
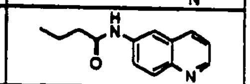
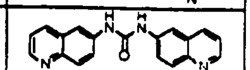
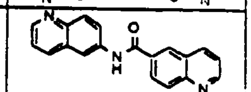
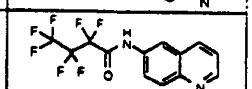
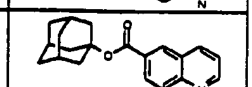
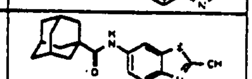
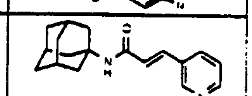
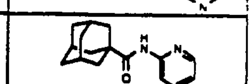
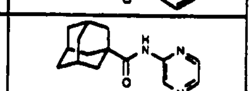
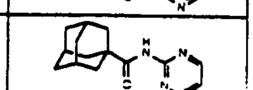
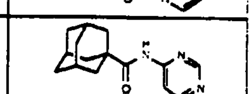
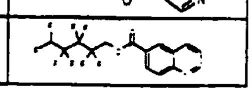
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	
60	
61	
62	
63	
64	
65	
66	
67	
68	

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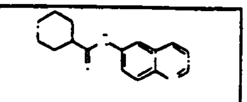
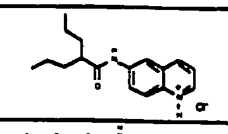
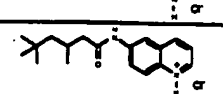
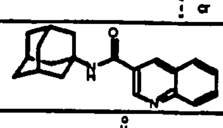
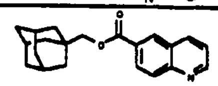
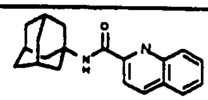
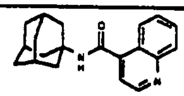
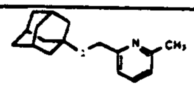
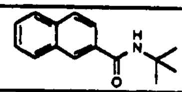
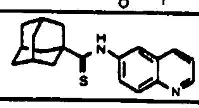
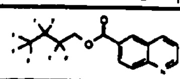
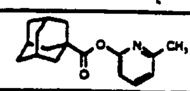
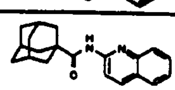
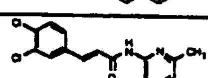
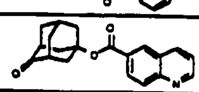
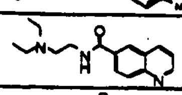
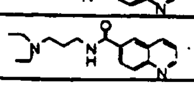
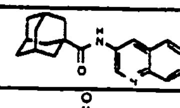
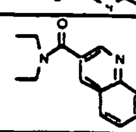
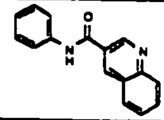
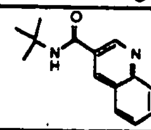
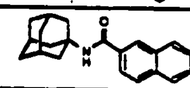
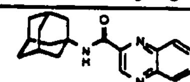
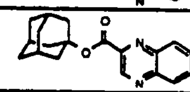
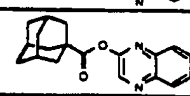
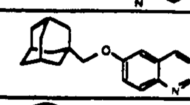
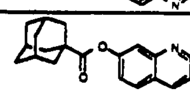
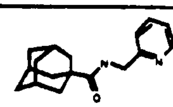
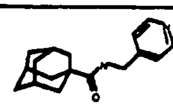
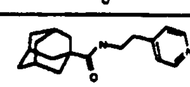
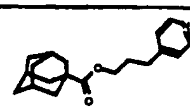
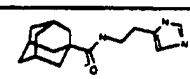
69	
70	
71	
72	
73	
74	
75	
76	
77	
78	
79	
80	
81	
82	
83	
84	
85	
86	
87	
88	
89	
90	
91	
92	
93	
94	
95	
96	
97	
98	
99	
100	

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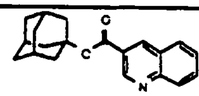
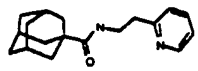
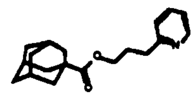
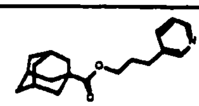
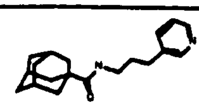
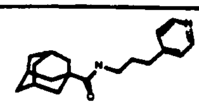
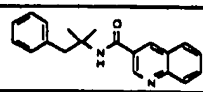
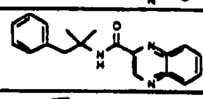
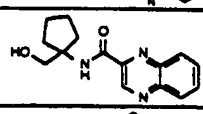
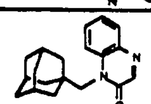
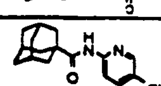
101..	
102	
103	
104	
105	
106	
107	
108	
109	
110	
111	
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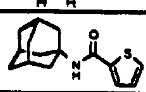
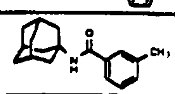
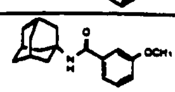
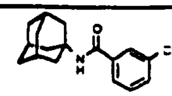
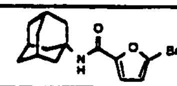
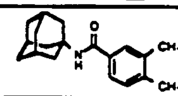
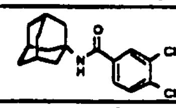
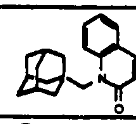
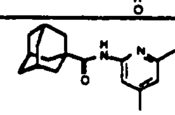
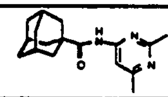
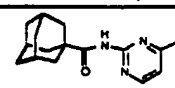
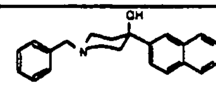
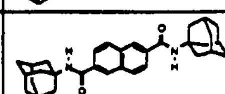
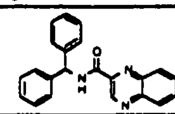
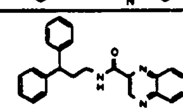
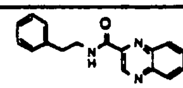
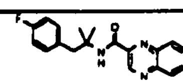
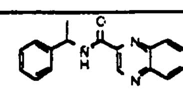
113	
114	
115	

116	
117	
118	
119	
120	
121	
122	
123	
124	
125	
126	
127	
128	
129	
130	

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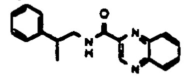
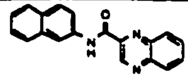
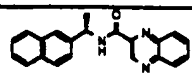
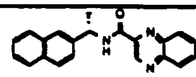
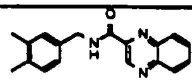
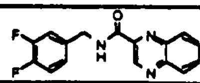
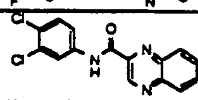
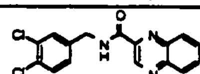
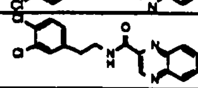
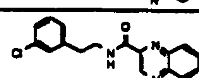
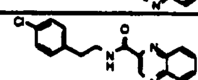
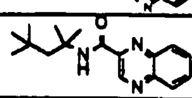
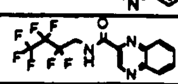
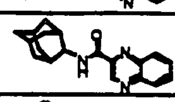
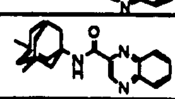
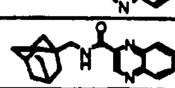
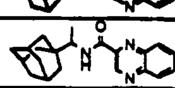
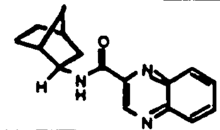
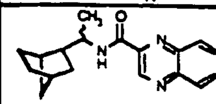
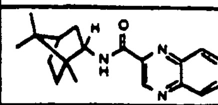
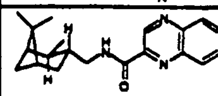
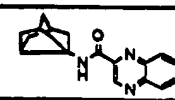
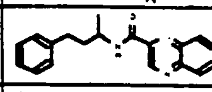
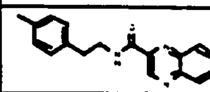
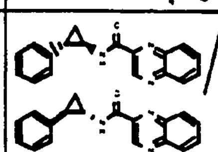
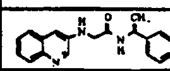
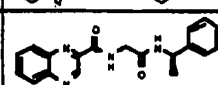
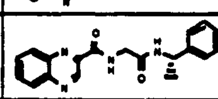
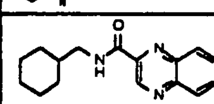
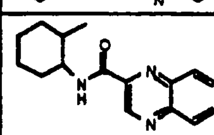
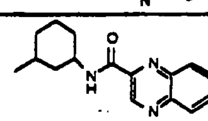
131	
132	
133	
134	
135	
136	
137	
138	
139	
140	
141	
142	
143	
144	
145	
146	
147	

148	
149	
150	
151	
152	
153	
154	
155	
156	
157	
158	
159	
160	
161	

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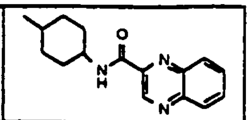
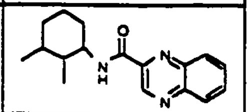
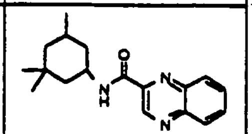
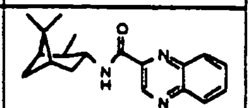
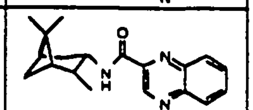
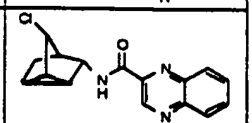
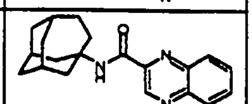
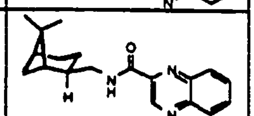
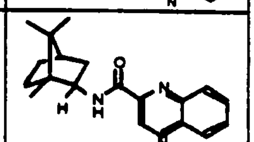
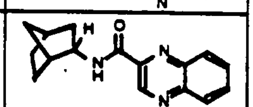
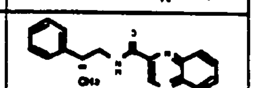
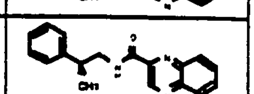
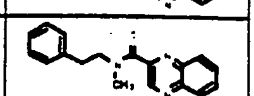
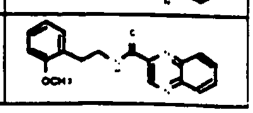
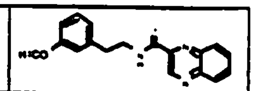
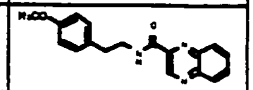
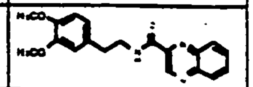
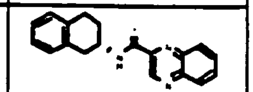
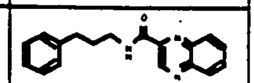
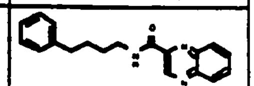
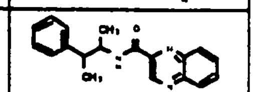
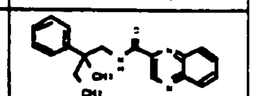
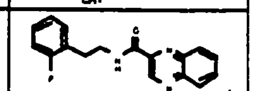
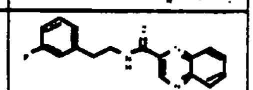
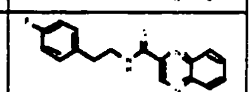
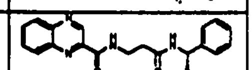
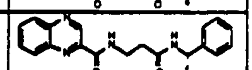
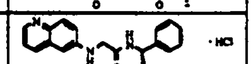
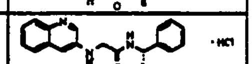
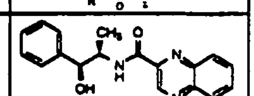
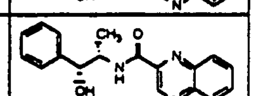
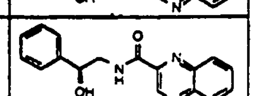
162	
163	
164	
165	
166	
167	
168	
169	
170	
171	
172	
173	
174	
175	

176	
177	
178	
179	
180	
181	
182	
183	
184	
185	
186	
187	
188	
189	
190	
191	
192	
193	

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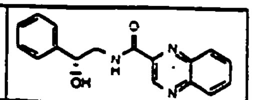
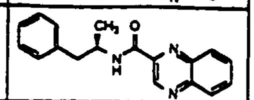
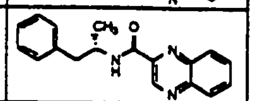
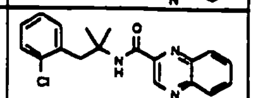
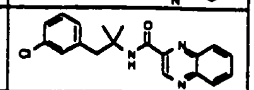
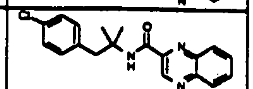
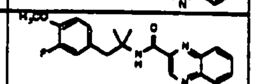
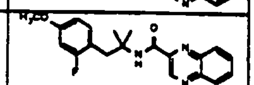
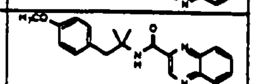
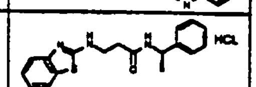
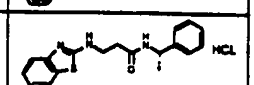
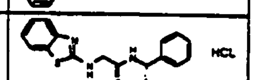
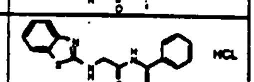
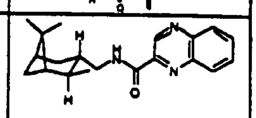
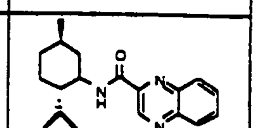
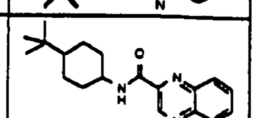
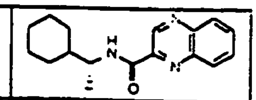
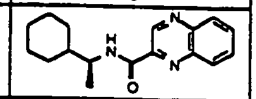
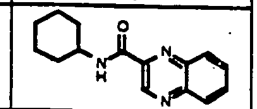
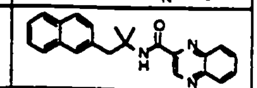
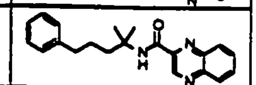
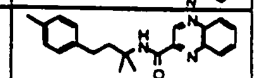
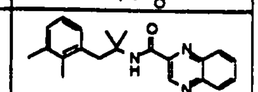
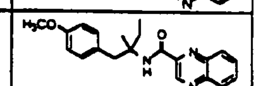
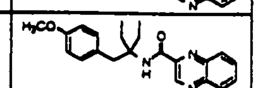
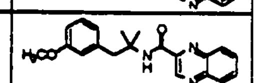
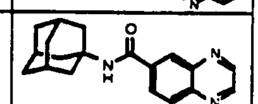
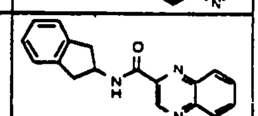
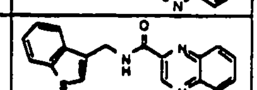
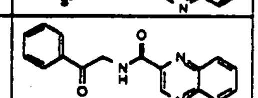
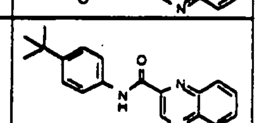
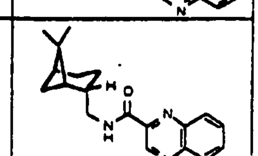
194	
195	
196	
197	
198	
199	
200	
201	
202	
203	
204	
205	
206	
207	
208	
209	
210	
211	
212	
213	
214	
215	
216	
217	
218	
219	
220	
221	
222	
223	
224	
225	

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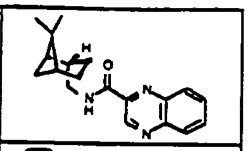
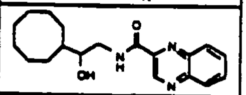
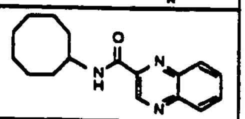
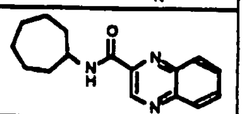
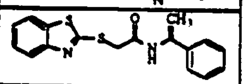
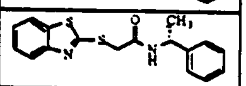
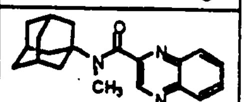
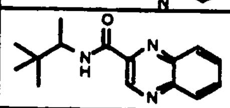
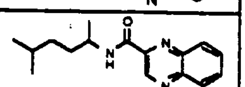
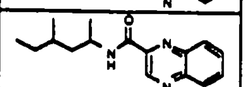
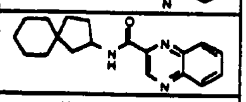
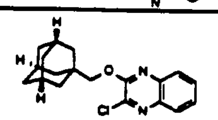
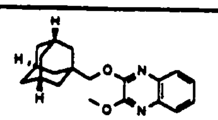
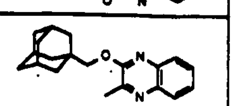
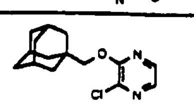
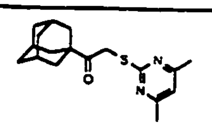
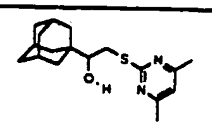
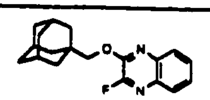
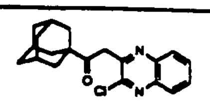
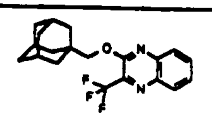
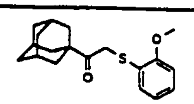
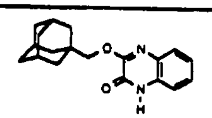
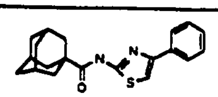
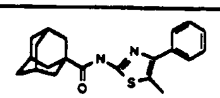
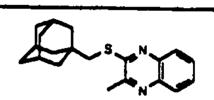
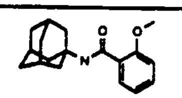
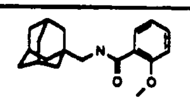
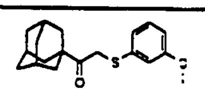
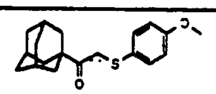
226	
227	
228	
229	
230	
231	
232	
233	
234	
235	
236	
237	
238	
239	
240	

241	
242	
243	
244	
245	
246	
247	
248	
249	
250	
251	
252	
253	
254	

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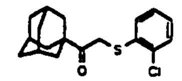
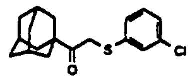
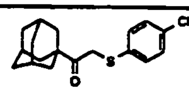
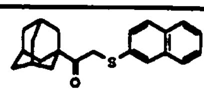
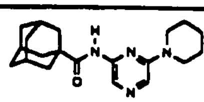
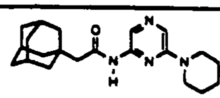
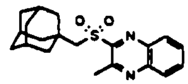
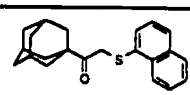
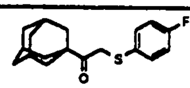
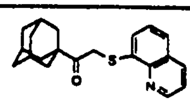
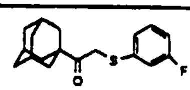
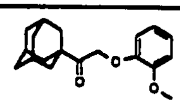
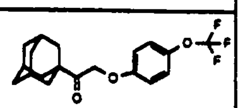
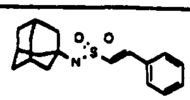
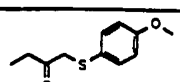
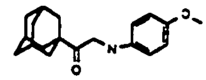
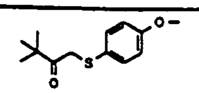
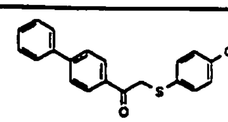
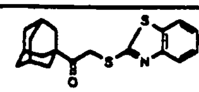
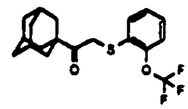
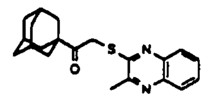
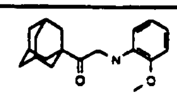
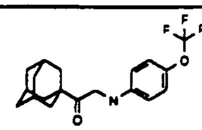
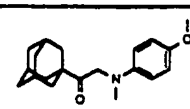
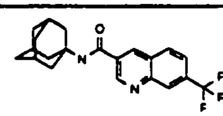
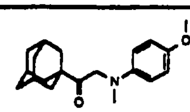
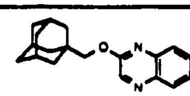
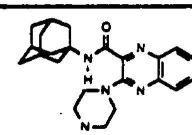
255	
256	
257	
258	
259	
260	
261	
262	
263	
264	
265	
266	
267	
268	
269	

270	
271	
272	
273	
274	
275	
276	
277	
278	
279	
280	
281	
282	

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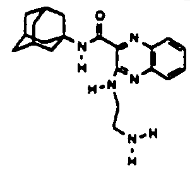
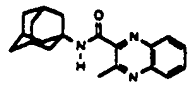
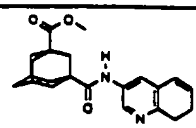
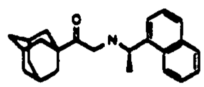
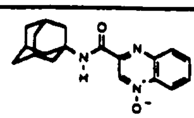
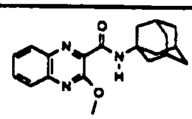
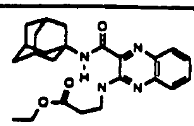
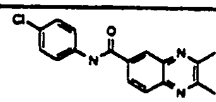
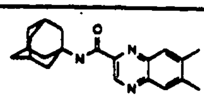
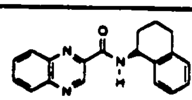
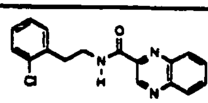
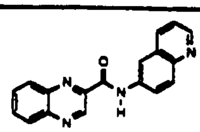
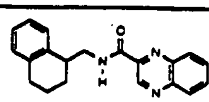
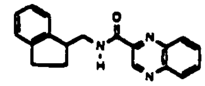
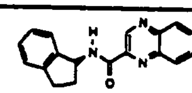
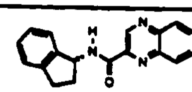
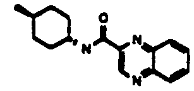
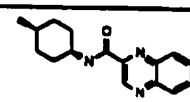
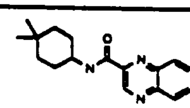
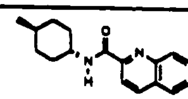
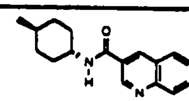
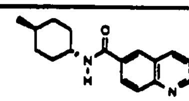
283	
284	
285	
286	
287	
288	
289	
290	
291	
292	
293	
294	
295	

296	
297	
298	
299	
300	
301	
302	
303	
304	

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